Paid Circulation, 23,887

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 239 · SEPTEMBER 2, 1948 · NUMBER 10

The Role of Sodium in the Production of Edema 353
John P. Peters

Nail Changes in Functional and Organic Arterial Disease 362
Edward A. Edwards

A Postoperative Mastectomy Dressing 366
Leo H. Pollock

Favism 367
Albert P. Rosen and James J. Scanlan

Medical Progress: Pregnancy Tests (Concluded) 369
Stanley L. Robbins

Case Records of the Massachusetts General Hospital 373

Editorials:

England Abandons Compulsory Vaccination 379

Progress in the Treatment of Leprosy 380

Professor Neuburger in America 381

Storrow House 382

Massachusetts Medical Society 382

Notices 382

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.

Working Together for a Healthier World

In health matters, people place their reliance on the medical and closely allied professions. Each of these is essential to the orderly and efficient application and distribution of vital medical services and supplies. Eli Lilly and Company co-operates fully with qualified groups. Through working together, the medical and related professions have raised standards of health the world over.

Lilly

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

MASSACHUSETTS MEDICAL SOCIETY

OFFICERS AND STANDING COMMITTEES

President
Daniel B. Reardon, Quincy

President-Elect
Arthur W. Allen, Boston

Vice-President
Donald Munro, Boston

Secretary
H. Quimby Gallupe, Waltham

Treasurer
Eliot Hubbard, Jr., Cambridge

Assistant Treasurer
Norman A. Welch, West Roxbury

Orator
C. Sidney Burwell, Brookline

Delegates to American Medical Association
Charles J. Kickham, Brookline; Leland J. McKittrick, Brookline; Patrick J. Sullivan, Dalton; John J. Curley, Leominster; Walter G. Phippen, Salem; Frank W. Snow, Newburyport.

Director of Medical Information and Education
John F. Conlin, Boston

Executive Secretary
Robert St. B. Boyd, Boston

Executive Offices, 8 Fenway, Boston 15, Telephone KE 6-5162

Committee on Publications
Chairman, Richard M. Smith; Oliver Cope, John Fallon, James P. O'Hare, Conrad Wesselhoeft.

Committee on Arrangements
Chairman, Harold G. Giddings; John W. Norcross, Franklin G. Balch, Jr., Gordon Donaldson, Albert Ehrenfried.

Committee on Ethics and Discipline
Chairman, Ralph R. Stratton; William J. Brickley, Archibald R. Gardner, Fred R. Jouett, Allen G. Rice.

Committee on Medical Education
Chairman, Chester S. Keefer; James M. Faulkner, George D. Henderson, Isaac R. Jankelson, Robert T. Monroe.

Committee on Membership
Chairman, Lewis S. Pilcher; William A. R. Chapin, Peirce H. Leavitt, Francis P. McCarthy, Samuel N. Vose, John E. Moran,* Kathleyne S. Snow,* Bancroft C. Wheeler.*

*Representing the supervising censors.

Committee on Public Health
Chairman, Roy J. Ward; John J. Poutas, Warren R. Sisson, Lawrence J. Smith, Conrad Wesselhoeft.

Committee on Medical Defense
Chairman, Horatio Rogers; Edwin D. Gardner, Charles J. Kickham, John E. Moran, William R. Morrison.

Committee on Society Headquarters
Chairman, Frank R. Ober; Albert A. Hornor, Walter G. Phippen, George L. Steele.

Committee on Finance
Chairman, Robert W. Buck; Francis C. Hall, Fabyan Packard, Bancroft C. Wheeler, Charles F. Wilinsky.

Committee on Industrial Health
Chairman, Daniel L. Lynch; Joseph C. Aub, Louis R. Daniels, John C. Downing, Harold R. Kurth, Frederic N. Manley, Henry C. Marble.

OFFICERS OF THE SECTIONS

Medicine
Chairman, Laurence B. Ellis, Cambridge; *vice-chairman*, Allen S. Johnson, Longmeadow; *secretary*, James A. Halsted, Dedham.

Surgery
Chairman, Robert E. Gross, Boston; *secretary*, Franklin G. Balch, Jr., Boston; EXECUTIVE COMMITTEE — J. Hartwell Harrison, Brookline.

Pediatrics
Chairman, W. Bradford Adams, Springfield; *secretary*, Gerald N. Hoeffel, Boston.

Obstetrics and Gynecology
Chairman, James F. Conway, Brookline; *vice-chairman*, Daniel J. McSweeney, Boston and Milton; *secretary*, Duncan E. Reid, Boston.

Radiology
Chairman, Albert M. Moloney, Boston; *secretary*, Lawrence Robbins, Boston.

Physiotherapy
Chairman, David C. Ditmore, Boston; *secretary*, Arthur L. Watkins, Boston.

Dermatology and Syphilology
Chairman, Francis P. McCarthy, Boston; *secretary*, Alfred Hollander, Springfield.

Anesthesiology
Chairman, Morris J. Nicholson, Boston; *secretary*, Jacob Fine, Beverly.

OFFICERS OF THE DISTRICT MEDICAL SOCIETIES FOR 1948–1949

BARNSTABLE — *President*, Henry P. Hopkins, Chatham; *vice-president*, Arthur J. D'Elia, Harwichport; *secretary*, Frederick Sanborn, Osterville; *treasurer*, Frank Travers, Barnstable; *librarian*, Carroll H. Keene, Chatham; *executive* and *public-relations councilor*, Paul P. Henson, Hyannis; *legislative councilor*, Julius G. Kelley, Pocasset.

BERKSHIRE — *President*, George S. Reynolds, Pittsfield; *vice-president*, N. B. McWilliams, Williamstown; *secretary*, Daniel N. Beers, Pittsfield; *treasurer*, Theodore W. Jones, Pittsfield; *executive councilor*, Helen M. Scoville, Pittsfield; *public-relations councilor*, Patrick J. Sullivan, Dalton; *legislative councilor*, John Hughes, Pittsfield.

BRISTOL NORTH — *President*, Joseph V. Chatigny, Taunton; *vice-president*, James H. Brewster, Attleboro; *secretary*, William E. Dawson, Taunton; *treasurer*, Charles E. Hoye, Taunton; *executive councilor*, Joseph L. Murphy, Taunton; *public-relations councilor*, Milton E. Johnson, Attleboro; *legislative councilor*, William M. Stobbs, Attleboro.

BRISTOL SOUTH — *President*, Aubrey J. Pothier, New Bedford; *vice-president*, John S. Fielden, Fall River; *secretary* and *treasurer*, James E. Fell, Fall River; *executive councilor*, Richard B. Butler, Fall River; *public-relations councilor*, Harold E. Perry, New Bedford; *legislative councilor*, Curtis C. Tripp, New Bedford.

ESSEX NORTH — *President*, Robert E. Blais, Amesbury; *vice-president*, Z William Colson, Lawrence; *secretary* and *public-relations councilor*, Harold R. Kurth, Lawrence; *treasurer*, J. Leroy Wood, Lawrence; *librarian*, Frank W. Stockwell, Newburyport; *executive councilor*, Rolf C. Norris, Methuen; *legislative councilor*, Nicandro F. DeCesare, Lawrence.

ESSEX SOUTH — *President*, Edward L. Peirson, Salem; *vice-president*, Burleigh B. Mansfield, Ipswich; *secretary*, Henry D. Stebbins, Salem; *treasurer*, Andrew Nichols, 3rd, Danvers; *executive councilor*, Albert E. Parkhurst, Beverly; *public-relations councilor*, Bernard Appel, Lynn; *legislative councilor*, Loring Grimes, Swampscott.

FRANKLIN — *Presidents* and *executive councilor*, Lawrence R. Dame, Greenfield; *vice-president*, Perrin N. Freeman, Greenfield; *secretary* and *treasurer*, Milton M. Sisson, Greenfield; *public-relations councilor*, John E. Moran, Greenfield; *legislative councilor*, Harold R. Mahar, Orange.

HAMPDEN — *President*, Robert Hildreth, Westfield; *vice-president* and *legislative councilor*, Arthur Riordan, Springfield; *secretary* and *treasurer*, Walter Williams, Springfield; *executive councilor*, Archibald Douglas, Westfield; *public-relations councilor*, Frederic Hagler, Springfield.

HAMPSHIRE — *President*, Edward J. Manwell, Northampton; *vice-presidents*, Henry Tadgell, Belchertown; *secretary* and *treasurer*, F. Mary P. Snook, Worthington; *librarian*, Abbie M. O'Keefe, Northampton; *executive councilor*, Maurice Kennedy, Hadley; *public-relations councilor*, Joseph R. Hobbs, Williamsburg; *legislative councilor*, Justin E. Hayes, Northampton.

MIDDLESEX EAST — *President*, Milton J. Quinn, Winchester; *vice-president*, Ira W. Richardson, Wakefield; *secretary*, Roy W. Layton, Melrose; *treasurer*, Charles W. DeWolf, Wakefield; *librarian*, Angelo L. Maietta, Winchester; *executive councilor*, Kenneth L. Maclachlan, Melrose; *public-relations councilor*, Milton J. Quinn, Winchester; *legislative councilor*, Justin L. Anderson, Reading.

MIDDLESEX NORTH — *President*, James Y. Rodger, Lowell; *vice-president*, Harry Coburn, Lowell; *secretary*, Brendan D. Leahey, Lowell; *treasurer*, Mason D. Bryant, Lowell; *executive councilor*, William M. Collins, Lowell; *public-relations councilor*, Samuel A. Dibbins, Lowell; *legislative councilor*, Joseph Sweeney, Lowell.

MIDDLESEX SOUTH — *Presidents*, John F. Casey, Allston; *vice-president*, James Marvin Baty, Belmont; *secretary*, Alexander A. Levi, Newton; *treasurer*, Fabyan Packard, Belmont; *orator*, Alfred O. Ludwig, Belmont; *executive councilor*, Joseph C. Merriam, Framingham; *public-relations councilor*, Ralph H. Wells, Lexington; *legislative councilor*, Kenneth J. Tillotson, Belmont.

NORFOLK — *President*, George W. Papen, Brookline; *vice-president*, W. Richard Ohler, Jamaica Plain; *secretary*, Basil E. Barton, West Roxbury; *treasurer*, Albert Ehrenfried, Brookline; *executive councilor*, Charles J. E. Kickham, Jamaica Plain; *public-relations councilor*, Dean S. Luce, Canton; *legislative councilor*, Solomon L. Skvirsky, Brighton.

NORFOLK SOUTH — *President*, Frederick Hinchliffe, Cohasset; *vice-president*, Edmund B. FitzGerald, Wollaston, *secretary* and *librarian*, Ebenezer K. Jenkins, South Braintree; *treasurer*, Raymond G. Vinal, Norwell; *executive councilor*, Robert L. Cook, Quincy; *public-relations councilor*, Henry A. Robinson, Hingham; *legislative councilor*, David L. Belding, Hingham.

PLYMOUTH — *President*, George A. Buckley, Brockton; *vice-president*, Mildred L. Ryan, Brockton; *secretary*, Samuel Gale, Brockton; *treasurer*, Henry Rabnowitz, Brockton; *librarian*, John H. Weller, Bridgewater; *executive councilor*, George A. Moore, Brockton; *public-relations councilor*, Charles D. McCann, Brockton; *legislative councilor*, Alfred L. Duncombe, Brockton.

SUFFOLK — *President*, Alexander J. A. Campbell, Brighton; *vice-president*, Lawrence J. McCarthy, Chelsea; *secretary*, Charles G. Shedd, Wellesley; *treasurer*, Sidney C. Wiggin, Waban; *executive councilor*, Harvey A. Kelly, Winthrop; *public-relations councilor*, Howard F. Root, Boston; *legislative councilor*, William E. Browne, Boston.

WORCESTER — *President*, John J. Dumphy, Worcester; *vice-president*, Bancroft C. Wheeler, Worcester; *secretary*, Donald Hight, Worcester; *treasurer*, Arthur D. Ward, Worcester; *librarian*, Philip H. Cook, Worcester; *executive councilor*, John Fallon, Worcester; *public-relations councilor*, Nicholas S. Scarcello, Worcester; *legislative councilor*, John B. Butts, Worcester.

WORCESTER NORTH — *President*, Donald B. Cheetham, Athol; *vice-presidents* and *legislative councilor*, C. Bertram Gay, Fitchburg; *secretary*, James G. Simmons, Fitchburg; *treasurer*, Frederick H. Thompson, Jr., Fitchburg; *executive councilor*, John J. Curley, Leominster; *public-relations councilor*, James V. McHugh, Leominster.

The New England
Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 239 SEPTEMBER 2, 1948 Number 10

THE ROLE OF SODIUM IN THE PRODUCTION OF EDEMA*

JOHN P. PETERS, M.D.†

NEW HAVEN, CONNECTICUT

THE term "edema" is applied to swellings produced by excessive accumulation of extracellular fluid without definite bounding membranes. These may be local or general. They are usually, but not always, associated with expansion of the total extracellular fluid of the body. They are even more loosely correlated with the total amount of water in the body. The simplest example of the formation of edema without change of the volume of fluid in the body is the swelling of the feet of a subject who stands still or rests in a relaxed position against a board at an angle of 60°. It is of the utmost importance in the analysis of edema to distinguish between the influence of exchanges between the body and the external environment on the one hand, and the distribution of fluid within the body on the other.

Although the extracellular fluid is more or less continuous, the distribution of this fluid need not be uniform. Pools of edema may occur because of local disturbances of the forces that determine the formation and removal of extracellular fluid. For example, in lymphedema fluid containing a high concentration of protein accumulates in the lower extremities because the lymphatic vessels are obstructed. If the subject is placed in the recumbent position with feet elevated, the fluid seeps into the flanks, which may become temporarily edematous.

The principal components of the extracellular fluid are sodium salts, chiefly the chloride, and water. The proportions of these components, which can diffuse freely throughout the extracellular fluid, are sedulously preserved by means discussed below. The accumulation of edema is limited, therefore, by the supply of either salt or water.

Motions of fluid between the blood capillaries and the adjacent spaces are governed, as Starling[1] showed, by the balance between two opposing forces, hydrostatic pressure and colloid osmotic pressure. In the simplest concept of the principle, the force driving fluid from the capillaries is the blood pressure in these vessels; the force driving or drawing water back into the blood stream is the osmotic pressure of the proteins, and especially albumin, which has a smaller molecular size than globulin. Such a simplified concept assumes that the fluid about the capillaries contains no protein and is under no hydrostatic pressure. Actually, this fluid does contain variable amounts of protein and is under a certain hydrostatic pressure, the elasticity of the tissues, or tissue tension. The equilibrium between blood and extracellular fluid is, therefore, more precisely defined as follows: transudation is favored by capillary blood pressure and colloid osmotic pressure of perivascular fluid and opposed by colloid osmotic pressure of plasma and by tissue tension; factors that contribute to tissue tension are inherent inelasticity of tissues and distention of tissues by fluid because of imbalance of capillary-tissue exchange and variations of lymphatic drainage.

It is thus evident that the tendency to transudation cannot be correlated directly with either capillary blood pressure or serum albumin alone. Nevertheless, the applicability of the Starling principle to the formation of edema in a variety of conditions has been challenged because the presence and magnitude of edema is not directly correlated with either or both of these forces. The validity of this theory does not rest upon physical measurements of capillary blood pressure and colloid osmotic pressure. It follows naturally from thermodynamic laws if the composition of extracellular fluid is identical with that of an ultrafiltrate of plasma, which has been demonstrated by abundant evidence. The brilliant experiments of Krogh, Landis and others proved that hydrostatic pressure and colloid osmotic pressure in particular systems of the body are susceptible to accurate measurement. With present knowledge it can be asserted that if these measurements had been incompatible with the Starling principle, it would have been a reflection upon the measurements, not the principle.

It is fundamental to a critical evaluation of the formation of edema that physiologic and clinical

*Presented at a meeting of the Boston City Hospital House Officers Association, Boston, April 20, 1948.

†John Slade Ely Professor of Medicine, Yale University School of Medicine.

hypotheses dealing with this process be compatible with basic mathematical, physical and chemical laws. If the simple relation between the concentration of serum albumin and transudation from the blood stream appears to be violated, conditions of equilibrium must be more carefully examined. One reason for discrepancies is the fact that capillary blood pressure is not uniform throughout the blood stream. Its measurement in the intact animal in any part of the blood stream is difficult; in most parts it is impossible. It must never be confused with arterial pressure, with which it may even be inversely related under certain circumstances. It is more closely, but not precisely, related to venous pressure, which is notoriously subject to local variations. Although the colloid osmotic pressure of the blood plasma is relatively uniform throughout the blood stream, the colloid osmotic pressure and the hydrostatic pressure of the extracellular fluid are subject to local variations and are not everywhere susceptible to measurement. Finally, the Starling exchange is not the only means by which fluid can escape from the extracellular spaces; the lymph channels provide an alternate route. Drinker and others have shown that the flow of lymph in normal lymphatic vessels is accelerated whenever transudation from the capillaries increases. One of the forces responsible for this accelerated flow is presumably increased tissue pressure.

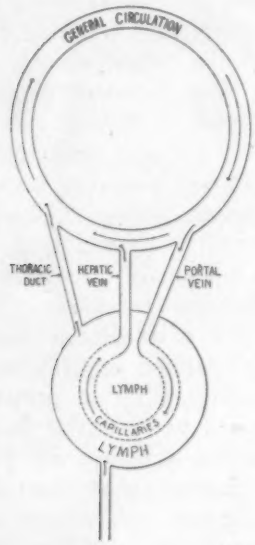

FIGURE 1. *Schematic Representation of the Circulation. The broken lines of the capillary walls in the portal circulation indicate that these vessels are permeable to protein.*

Normally, peripheral capillaries appear to be so impervious that extracellular fluid or subcutaneous edema fluid is almost free from protein. The small amounts of protein in normal extracellular fluid may be attributed to constant slight seepage through the capillary walls, possibly with contributions from the cells bathed by this fluid. This protein cannot return to the circulation through the intact capillary walls, but is taken up selectively by the lymphatic vessels. This explains the stubborn character of lymphatic edema and the high concentrations of protein found in such fluid. Unfortunately, neither the volume nor the flow of lymph can be measured.

In certain parts of the circulation, especially the liver and portal circulation, the vessels appear to be regularly and of necessity more permeable to protein.[1, 2] This was first demonstrated by Starling,[1] who recognized that the blood pressure in the portal vein is so low that if there were not protein in the fluid about the capillaries in this region the tissues would become completely desiccated. There must be in these regions a continuous circulation of protein from blood stream to extracellular fluid and back through the lymphatic vessels and the thoracic duct to the blood stream. This has been demonstrated by means of foreign proteins and various materials that adhere to or combine with protein.

Among these materials are the dyes, including Evans blue (T–1824), employed for the measurement of circulating plasma volume.[3] These dyes are retained in the blood stream, not by their molecular size, but because they combine with albumin. Within five minutes of its injection into the blood stream Evans blue can be detected in high concentration in thoracic-duct lymph.[4, 5] This being true, no refinement of colorimetric technics and no mathematical manipulations can make it an accurate measure of the circulating plasma. Always it must measure, in addition to the circulating plasma, part of the extracellular fluid into which it penetrates. If the volume of this extra circuit were constant and proportional to that of the circulating blood, and if the proportion of protein to water in it bore a constant relation to those in the plasma, the method might serve for the measurement of changes in plasma volume. But there is reason to believe that these factors are highly variable. If the protein and dye that escaped from the circulation were irrevocably lost, such a relative plasma volume could be estimated by mathematical extrapolation. But this system, so aptly devised for the well-being of the animal, was so damnably conceived to thwart the physiologist that part, and only a variable part, of the protein and dye is returned to the circulation again through the thoracic duct. The chief variables encountered in measurements of plasma volume by the dye method are as follows: those that are always operative include time of mixing and distribution in the blood stream, escape from the blood stream, return to the blood stream by lymph and permanent removal from plasma and lymph;

those that are sometimes operative comprise variations of circulating blood volume during a test, variations of volume of the thoracic-duct lymph system (that part of the extracellular fluid, drained by the thoracic duct, into which the dye penetrates) and variations of flow of the thoracic-duct lymph during a test. Since all are uncontrollable and unmeasurable, it should be evident to reasoning persons that the method can have no real value. A rather naïve diagram (Fig. 1) has been devised to illustrate this point in another way. The large circle above represents the general circulation, impervious to protein. Below is a shunt through the portal circulation, which contains a capillary bed, the broken outlines of which indicate that it is pervious to protein. This lies in a compartment representing the region drained by the thoracic duct. If the volume of the portal capillary bed merely expanded, without any increase of the total circulating fluid, the volume of plasma measured by the dye method would not change, although the amount of blood available to organs supplied by the general circulation would be reduced. If, when the portal capillary bed expanded, an equal volume of fluid entered the circulation, the volume of circulating plasma would increase, although only the usual amount would be available for organs in the general circulation. Thus far the dye method would give no misinformation about changes of circulating plasma volume. If, without any change of volume in the system, loss of protein and dye from the portal capillaries increased, the plasma volume by the dye method would seem to expand. This specious appearance of expansion would be greatly exaggerated if, at the same time, the thoracic-duct lymph compartment became larger.

In view of these considerations there should be no surprise that measurements by means of radioactive red blood cells or by carbon monoxide, which attaches itself to red blood cells, give smaller, and I should say more reasonable, values than dyes for changes of blood volume in pathologic or disturbed physiologic states.[6, 7] Granted that red blood cells are not evenly distributed throughout the circulation, an unevenness that has, I believe, been grossly exaggerated, this will not correct the errors inherent in the dye methods. It merely invalidates the only alternative methods. These technical details have been discussed at length because a large body of physiologic and clinical theory dealing with circulatory disorders and fluid exchanges depends for its validity largely upon measurements of blood volume by dye methods.

The exchange of water between the extracellular fluid and the cells appears to be controlled almost entirely by the osmotic pressure of electrolytes in the extracellular fluid, which, in turn, depends mainly upon the concentration of sodium in the fluid. This can be roughly symbolized by the equation

$$\frac{\text{Volume of E}}{\text{Volume of I}} \propto \frac{\text{Osmotic Pressure E}}{\text{Osmotic Pressure I}} \propto \frac{([Na] + [K])E}{([Na] + [K])I}$$

in which E and I represent extracellular and intracellular fluids respectively. The relative proportions of extracellular and intracellular fluid vary with the relative osmotic pressures of these fluids, which, in turn, depend upon the concentrations in the two mediums of those osmotically active components to which the cellular membranes are impervious. These are mainly sodium and potassium. The chief variable among these is the sodium of the extracellular fluid, which is, therefore, the principal determinant of the relative volume of the intracellular fluid. When the concentration of sodium falls the cells take up water and swell. When the concentration of sodium rises, the cells give up water and contract.

To form the 1000 to 1500 cc. of urine ordinarily excreted by a normal person in a day, Smith[4] has estimated that about 180 liters of water must be filtered through the glomeruli in the course of twenty-four hours. With this fluid are filtered about 24,000 milliequivalents of sodium and 20,000 of chloride to yield 80 to 180 milliequivalents of sodium chloride in the urine. This means that more than 99 per cent of the water and a still larger proportion of the sodium and chloride from the glomerular filtrate must be reabsorbed in its passage down the tubules. This process of reabsorption is so regulated that reabsorption of sodium, chloride and water can be varied independently.

The various steps in this process of reabsorption have been partly elucidated by direct analyses of mammalian tubular fluid made by Walker et al.[8] in Richards's laboratory and by inferential evidence adduced by Shannon[9] and others. Attention will be centered on sodium salts and water. It need only be said about urea that its excretion is roughly proportional to filtration and requires a certain proportion of water. Reabsorption of water is therefore limited by the concentration of urea in the glomerular filtrate, which is, in turn, directly proportional to the rate of nitrogen metabolism and the concentration of urea in the blood. Sodium and chloride, on the other hand, can be almost or quite completely reabsorbed from the tubules.

The reabsorptive process is tentatively outlined in Table 1. As the 180 liters of isotonic glomerular filtrate pass through the proximal tubules, about 60 to 80 per cent of the water, all the glucose and fractions of other solutes are removed, together with a roughly equivalent amount of sodium and chloride. There remains an isotonic solution in which the ratio of sodium to chloride, originally about 1.3:1, has become 1:1 — that is, the sodium bicarbonate has been reabsorbed, leaving prac-

tically all the remaining sodium as sodium chloride, together with the other solutes that will ultimately be found in the urine. In the loop of Henle a variable amount of sodium chloride is withdrawn. Obviously this is not withdrawn in solid form as the table suggests, but always in this step far more salt than water is reabsorbed. This leaves a hypotonic solution. Finally, in the terminal convoluted tubules water is abstracted to yield the fully elaborated urine, which is usually hypertonic.

Table 1. *The Process of Reabsorption.*

Site of Action	Solution	Volume	Sodium	Chloride	Ratio of Sodium to Chloride	Urea Nitrogen
		liters	*m.m.*	*m.m.*		*gm.*
Glomerular filtrate	Isotonic	180.0	24,000	20,000	1.25:1	24
Proximal convoluted tubules	Isotonic	54.0	7,600	7,600	1:1	—
Loop of Henle	Hypotonic	54.0	140	140	1:1	—
Terminal convoluted tubules	Hypertonic	1.5	140	140	1:1	12

If this description of the sequence of events is correct, sodium salts have a topographic priority over water in the process of reabsorption. Whether the sequence follows the order described or not, sodium salts have a functional priority over water and enjoy a greater degree of freedom. If an animal is deprived or depleted of sodium chloride these ions promptly disappear almost completely from the urine. The enormous quantities still provided to the tubules through the glomeruli are almost entirely reabsorbed. The administration of large amounts of water and procedures that alter the rate of glomerular filtration have no effect per se on the reabsorption of sodium chloride, although they may vary the volume of urine greatly. The terminal reabsorption of water, on the other hand, is limited by the quantity of solutes requiring excretion — that is, the quantity that escapes reabsorption in the proximal convoluted tubules and the loop of Henle. Among these are sodium salts. If, for any reason, these salts are not reabsorbed, the quantity of water that can be reabsorbed in the terminal process is proportionally reduced. Water, therefore, has an obligation to sodium salts that is not reciprocated. Moreover, water is similarly at the mercy of all solutes that find their way to the terminal segments of the tubules.

Since the reabsorption of both sodium salts and water involves the production of concentration gradients across the membranes of the tubular cells, these processes must require the expenditure of energy. If, therefore, the kidney is injured by disease, reabsorption of sodium chloride and water will diminish. In advanced renal insufficiency the ability of the kidneys to conserve both salt and water is impaired. This disability is manifested in polyuria. In this condition restriction of salt is contraindicated; it may even be advisable to give extra salt.

The terminal reabsorption of water appears to be controlled chiefly by the antidiuretic principle of the posterior pituitary hormone, which Heller[10] has succeeded in separating from the pressor principle. The presence in the urine of antidiuretic principle has been demonstrated not only in states of dehydration in which there is need to conserve water but also in a variety of pathologic conditions attended by edema: the nephrotic syndrome,[11] toxemias of pregnancy,[12] cirrhosis of the liver[13] and so forth. The obvious inference is that the oliguria of these conditions is partly or wholly induced through the influence of posterior pituitary activity. The obligation of water to sodium and the independent control of the two are illustrated by the action of the antidiuretic hormone. If this is given with a dose of water to an animal, the water will be almost entirely retained, though excretion of salt continues unchanged. If, on the other hand, the antidiuretic hormone is given with a dose of salt solution, it has little or no antidiuretic effect because the salt, which is not affected by the hormone, demands water for its excretion. Conversely, the administration of salt aggravates diabetes insipidus because the salt cannot be concentrated in the urine in the absence of the antidiuretic hormone.

The evidence concerning control of the reabsorption of sodium salts is less direct. Adrenalectomized animals and patients with Addison's disease tend to waste sodium in the urine. This wastage can be prevented by either cortical extract or desoxycorticosterone acetate. On the other hand, cortical extracts have no pronounced effect upon the excretion of salt by the intact animal. The reabsorption of sodium is increased by desoxycorticosterone acetate, but this is not a natural adrenal steroid. It is, moreover, impossible to demonstrate changes in adrenocortical activity that are related to salt excretion. Nevertheless, from inferential evidence it is tentatively proposed that reabsorption of sodium salts is governed by a steroid secreted by the adrenal cortex.

Regardless of the specific principle that controls reabsorption of sodium, the conditions that influence it may be examined. When the concentration of sodium salts in the serum alone is varied by administration of different quantities of these salts with adequate amounts of water, the excre-

tion of sodium varies directly with its concentration in the serum. Such a relation cannot, however, be discerned under normal dietary conditions and can be strikingly disturbed by certain procedures. The reabsorption of sodium is powerfully affected by factors other than its concentration in the serum. Among these factors is the state of hydration (or some function of the state of hydration) of the subject. If an animal is deprived of all water, some sodium may be immediately lost in the urine, but, after only a short interval, the excretion of both sodium and chloride falls to a minimum. This causes their concentrations in the serum and extracellular fluids to rise.[14, 15] The same phenomenon may be observed when animals are dehydrated by diuretic measures, such as injection of sodium sulfate without adequate amounts of water. This behavior has obvious beneficial effects: by withdrawal of sodium chloride from the urine the animal is enabled to excrete other solutes with a smaller expenditure of water; and the accumulation of sodium chloride in the extracellular fluids raises the osmotic pressure of these fluids, thereby causing water to emerge from the cells. This protects the extracellular fluid from extinction and provides additional water for the formation of urine. By this reaction the water loss is distributed throughout the whole water of the body.

The most powerful known stimulus to the reabsorption of sodium appears to be the need to conserve water. At first sight it seems illogical that this need should express itself primarily through an action on sodium rather than water. If, however, salt were not reabsorbed, the antidiuretic hormone could not effectively limit the excretion of water. Moreover, the intracellular water would not be made available for the formation of urine.

Reabsorption of water — that is, activity of the antidiuretic hormone — appears to be promoted by an increase of the concentration of solutes, perhaps more specifically sodium salts, in the serum. This has been demonstrated directly by Verney.[16] It can also be inferred from the action of desoxycorticosterone acetate (Table 2). If this compound is injected into a normal animal that is given no water or only the usual amounts of water serum sodium rises. At the same time the excretion of water is retarded. The consequence is an increase of the concentration of sodium and of the total amounts of sodium and water in the extracellular fluids. Apparently when the sodium of the serum rises the urine volume is reduced by action of the antidiuretic hormone, just as it is in dehydration. The increased concentration of sodium in the serum also has the effect of stimulating thirst. If, then, the animal has free access to water, it will drink enough to dilute the serum sodium to the normal concentration. This, in turn, inhibits antidiuretic activity. The actual effect of an excess of desoxycorticosterone acetate, therefore, is to produce a state resembling diabetes insipidus. This differs, however, from posterior pituitary diabetes in several respects. In desoxycorticosterone diabetes insipidus the primary factor is thirst; in posterior pituitary diabetes insipidus it is polyuria. In the former the amounts of salt and water in the body are greater and in the postpituitary syndrome less, than normal. Although the desoxycorticosterone acetate syndrome is initiated by an increase in the amount of sodium in the body, so long as water is freely available the animal will drink enough water to keep the serum sodium normal or only slightly elevated. This point deserves emphasis: retention of sodium, if there is free access to water, because it stimulates thirst, is not associated with an excessive concentration of sodium in the serum. High serum sodium is almost invariably a sign of dehydration.

TABLE 2. *Comparison of Findings in Two Types of Diabetes Insipidus.*

POSTERIOR PITUITARY DIABETES	DESOXYCORTICOSTERONE DIABETES
Initial inhibition of reabsorption of water	Initial increase of reabsorption of sodium
Primary diuresis	Primary thirst
Deficient body water	Excess body water
Deficient body sodium	Excess body sodium

A patient with postpituitary diabetes, if deprived of water, will become dehydrated and will develop hypernatronemia and hyperchloremia. These disorders will be exaggerated if salt is given. This cannot easily be demonstrated in the clinic because withdrawal of water, especially if salt is given, is extremely distressing to such patients. We have recently encountered a striking example of this state. A young woman who had recently had a craniopharyngioma removed was admitted to the hospital because of headaches, dizziness, nausea, vomiting and confusion. Because of signs of increased intracranial pressure an exploration was immediately undertaken. A cyst, found in the third ventricle, was aspirated and removed. The patient withstood the operation surprisingly well. Besides a transfusion of 500 cc. of blood she was given 1000 cc. of physiologic saline solution and 1000 cc. of 10 per cent glucose solution intravenously. The next morning her pulse was rapid and her blood pressure low, but she was conscious and did not appear to be in shock. On inquiry it was found that she had voided 3000 cc. since the operation — more fluid than she had received, despite the dehydrating effect of the procedure and a moderate elevation of temperature. It was then discovered that her serum sodium, which had been 142 mm. (upper limit of normal) before the operation, had risen to 171 mm., with chloride

comparably elevated. It was obvious that she had developed acute diabetes insipidus. Since she could not take fluid this expressed itself in an extreme dehydration reaction. She was immediately given a continuous intravenous drip of glucose solution and intermittent injections of small amounts of pituitrin. The data are shown in Figure 2. Unfortunately the urine volume could not be recorded because urgency, together with her somnolent state, led to frequent

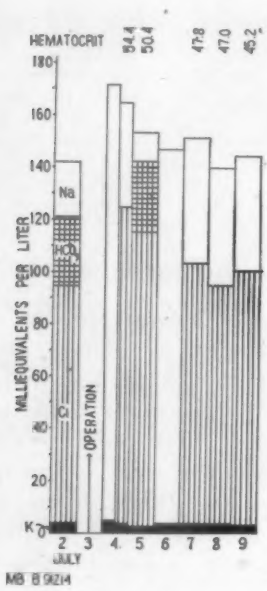

FIGURE 2. *Concentration of Electrolytes in the Serum of a Patient Who Developed Acute Diabetes Insipidus after Operation for the Removal of a Cyst in the Third Ventricle.*

involuntary urination in the bed. The polyuria could not be entirely controlled by pituitrin because of the side reactions produced by this preparation.

This is a long, but necessary, preamble to the discussion of edema, which is limited chiefly to the subject of cardiac edema, because this includes most of the features involved in edemas of every kind and because the present controversy about the subject is challenging. The sequence of events in the production of cardiac edema has been conventionally conceived as outlined in the left-hand column of Table 3.

According to this concept failure of the heart causes the blood to back up, increasing the venous pressure and thereby the capillary blood pressure. This provokes transudation of fluid from the capillaries with consequent reduction of the volume of circulating plasma. This last, in turn, provokes the kidneys to reabsorb more than the usual quantities of sodium salts and water. This seems a logical sequence, compatible with existing physiologic theory.

Because, they claim, retention of sodium precedes the rise of pressure, and because measurements by means of dyes indicate that the plasma volume does not contract, but rather expands, Warren and Stead[17] have proposed a reversed sequence, which they term "forward failure." According to this hypothesis the primary event is retention of sodium salts by the kidneys, which they attribute to some disturbance of the circulation to these organs. This leads to a similar retention of water. The consequent expansion of the volume of circulating plasma increases the capillary blood pressure, which, in turn, accelerates transudation and thus produces edema. From the standpoint of therapy the order of events is of great importance. The premises on which the theory of "forward failure" is based, therefore, require serious examination.

Those who would carry this theory so far as to suggest that the Starling principle is not operative in cardiac edema deserve no consideration, for

TABLE 3. *Origin of Cardiac Edema.*

STARLING[1]	STEAD[17]
1. Increased venous pressure and capillary pressure	1. Retention of salt and water
2. Transudation	2. Expansion of plasma volume
3. Hemoconcentration	3. Increased venous and capillary pressure
4. Retention of salt and water	4. Transudation

reasons mentioned above. Since the venous pressure is increased in heart failure at one time or another, there must be back pressure in the capillaries that will inevitably provoke transudation. Landis[18] has pointed out that this is not delayed until gross salt retention has occurred. Patients with minimal heart failure excrete sodium salts normally and remain free from edema when they are at rest in the recumbent position, but develop edema when they are erect with legs dependent. This formation of edema, as Perera[19] has shown, is attended by hemoconcentration.

If Stead is right, reasons must be found for expansion of the blood volume and simultaneous retention of sodium. The latter, it has been shown, is the characteristic reaction to the need to conserve water. Why, then, should it be called into play when there is an obvious excess of water in the body? The disorders encountered in disease may be regarded as normal physiologic responses to unusual conditions produced by pathologic processes. It is proper, then, to assume that retention of sodium in heart failure is provoked by the usual stimulus, the need to conserve water. This term must, however, be interpreted in terms of the kidneys: it cannot be the actual need to conserve water to which the kidneys respond, but conditions that lead the kidneys to believe that there is a need to conserve water. (This decision may, of course, be made in the adrenal cortex or some other organ,

rather than in the kidneys themselves, but this will not alter the nature of the argument.) The most crucial problem related to the formation of edema is the discovery of the criteria by which the kidneys determine whether to accelerate or retard the reabsorption of sodium.

Obviously, accumulation of fluid in the extracellular compartment is a matter of indifference to the kidneys. If it were not, they would dehydrate all the rest of the body in behalf of a milk leg or a lymphedema. On the contrary, they will reabsorb salt and water for the sake of the patient at large while the edema is forming. In these conditions, if water and salt are not given, the blood volume diminishes as the edema accumulates. Presumably, the kidneys, finding that fluid is escaping from the circulation, conclude that there is need to conserve water and therefore respond by reabsorbing more than the usual quantity of sodium salts.

The edema that accompanies hypoalbuminemia, whether this is referable to plasmapheresis, nutritive deficiencies or albuminuria, appears to originate in a similar manner. The sequence of events in all these states is as follows: escape of fluid from the circulation; retention of sodium and chloride; and retention of water. In terms of renal physiologic mechanisms implemented by their appropriate agencies, these processes are expressed as follows: the development of a serum albumin deficit causes a reduction of colloid osmotic pressure that results in the escape of fluid from the circulation; reduction of the circulating blood volume accelerates the reabsorption of sodium salts (presumably through the influence of increased secretion of an adrenal cortical hormone), resulting in the accumulation of sodium salts in the serum; and increased concentration of sodium in the serum causes thirst and accelerates reabsorption of water through increased secretion of posterior pituitary antidiuretic hormone, resulting in the retention of water, which, with the retained salt, produces edema.

TABLE 4. *Effect of Water and Salt on Edema.*

FACTOR	EFFECT ON SODIUM SALTS IN BODY	EFFECT ON ANTIDIURETIC ACTIVITY	EFFECT ON DEHYDRATION REACTION
Excess of water	Diluted	Inhibited	—
Limitation of water	Increased	Stimulated	—
Excess of sodium	Increased	Stimulated	Exaggerated
Limitation of sodium	Diminished	Diminished	Minimized

It is evident at a glance that if an "increase of capillary blood pressure" is substituted for "the development of a serum albumin deficit" the remainder of the sequence would follow unchanged (Table 4). If this sequence is in any large measure correct it has certain corollaries. First of all, the administration of water without salt should increase the edema but little, if at all, and by diluting the sodium salts in the extracellular fluid, it should inhibit the action of the antidiuretic hormone, permitting the water, but not the salt, to be excreted. Limitation of water, on the other hand, would have only a slight effect on the edema because it would increase the concentration of sodium salts in the serum, thereby stimulating antidiuretic activity. (Also, it would be a cruel measure because it would create intolerable thirst.) Administration of sodium salts would conduce to edema because it would exaggerate the dehydration reaction, thus stimulating antidiuretic activity. Restriction of sodium salts would minimize the dehydration reaction and the stimulus to antidiuretic activity. The term "dehydration reaction" is applied to reabsorption of sodium by the kidneys to conserve water. Essentially, this describes the behavior of patients with edema of either nephrosis or heart failure.

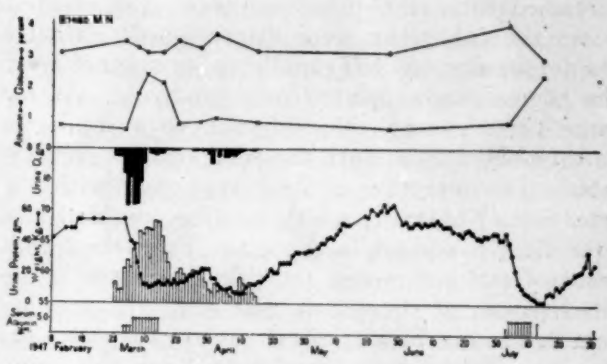

FIGURE 3. *Effect of Human Serum Albumin Injections upon the Edema of a Patient with a Nephrotic Syndrome.*
Concentrations of albumin and globulin in the serum are shown in the top segment of the figure. The arrows in the lower segment indicate injections of salt-poor human serum albumin. (The serum albumin was furnished by the Administrator of the National Blood Program, American Red Cross, on recommendation of the Subcommittee on Blood and Blood Derivatives of the Red Cross Medical Advisory Committee.)

If these phenomena were analyzed from the standpoint of exchanges of water and salt alone, the impression would be derived that the primary and initial reaction was retention of sodium, an impression that would gain additional support from the observation that mercurial drugs, which act by inhibiting the reabsorption of chloride, are effective diuretics in these forms of edema. The sequence that has been proposed is vividly illustrated by the effect of serum albumin in Figure 3. The patient, an eighteen-year-old girl in the nephrotic phase of a glomerular nephritis, had generalized edema that was resistant to salt restriction and the usual diuretic measures. Her serum albumin was less than 1 per cent. After a preliminary period of observation she was given daily intravenous injections of salt-poor human serum albumin, which

induced an excellent diuresis. By the end of six days she had lost 10.5 kg. (23.1 lb.). With this water a comparable quantity of chloride was excreted. At this point, when she was practically free from edema, further injections of albumin caused no further loss of weight or chloride. The immediate effect of the injections was to raise the serum albumin, which led to the absorption of fluid into the blood stream. Expansion of the circulating plasma was demonstrated by means of the hematocrit. The proteinuria, however, increased so greatly that the rise of serum albumin was not sustained after the injections were discontinued. After the injections were discontinued, although the serum albumin fell rapidly to its original level, the edema reaccumulated only gradually. At the same time urinary chloride sank to a minimum and remained there until the edema had reaccumulated. The retention of fluid kept pace with the retention of chloride, which may be considered as equivalent to sodium in this case. From the standpoint of salt and water, the primary factor in the development of the edema was salt. Its slow accumulation can be attributed to restriction of salt; water was at no time restricted. From this point of view the action of injections of albumin differs in no respect from that of mercurial diuretics, although its *modus operandi* is altogether dissimilar. Mercurial diuretics inhibit reabsorption of sodium, thereby removing the stimulus to antidiuretic activity. Albumin expands blood volume, thereby removing the stimulus to reabsorption of sodium salts.

Reduction of the volume of the circulating blood or plasma, therefore, appears to cause the kidneys to reabsorb salt in efforts to conserve water, even if there is an excessive amount of water in the body as a whole. Why, then, should the kidneys respond in a similar manner in heart failure if the blood volume in this condition is greater than normal? The presenting phenomena in fully developed heart failure are: excessive transudation from the blood stream, as evidenced by the presence of edema; increased venous and capillary blood pressures, which should tend to diminish the volume of the circulating plasma; and increased reabsorption of sodium by the kidneys, a reaction usually provoked by contraction of the volume of circulating plasma. There is reason to believe that the degree of expansion of the blood volume in heart failure has been exaggerated. Heart failure presents precisely that combination of disorders in which dye methods should be most unreliable, a condition in which the liver is distended with blood and fluids containing large amounts of protein and dye. The evidence for expansion of volume by other methods is not altogether consistent. Stewart[20] found that diuresis in heart failure occurred only if the specific gravity of the plasma fell. In an article by Merrill and Stead[21] the most striking instance of diuresis is associated with a sharp drop of hematocrit. In some of my own studies values for hemoglobin and hematocrit indicate hemoconcentration in heart failure. There is indubitable loss of fluid from the circulation in certain types of heart failure — namely, paroxysmal dyspnea and coronary occlusion. Stead and Ebert[22] are so impressed with the importance of expanded volume that they have advocated venesection for the treatment of the shock syndrome of coronary occlusion. That their patients died seems not to have dismayed them. Transfusions have been given to patients with the shock of coronary occlusion, with signal benefit.[23] Unfortunately, preconceptions so prevail that this life-saving measure is too often delayed until the shock has become irreversible.

If retention of sodium and consequent expansion of blood volume were the primary causes of cardiac edema, further expansion of blood volume should have a deleterious effect. This has not been satisfactorily demonstrated. Hypertonic glucose has been advocated for the treatment of heart failure under the pretext that the glucose was required by the heart muscle. Actually, it produces transitory hemodilution. McCann and Brown[24] induced diuresis in a patient with congestive heart failure by intravenous injection of concentrated human blood plasma. I have recently given injections of salt-poor human serum albumin to patients with heart failure. The cases thus far selected have been of a desperate type, mainly patients with advanced renal insufficiency as well as heart failure. Although no striking successes can be reported, dire forebodings of disaster have not been realized.

Granted that the circulating blood volume is expanded, if the reasoning concerning renal activity is logical, it must be so expanded that the kidneys are unaware of it or do not participate in it. It is not inconceivable that the circulating blood is pooled somewhere — for instance, in the liver and other viscera — and is thereby diverted from the kidneys. If expansion of blood volume is a response to such a dislocation of the circulation it should be regarded as a compensatory or protective reaction, even if it should prove to be misdirected. It may, of course, be not the actual volume of circulating plasma but some function usually related to the volume of circulating plasma — such as renal blood flow — that apprises the kidney of the need to conserve water.

This is not idle speculation. If the earlier physiologic argument has adhered to fact, the rationale for restriction of salt in both cardiac and nephrotic edema is clear. The relative ineffectiveness of limiting the intake of water is also explained. To be sure, edema cannot be formed without water, but the strongest physiologic stimulus to reabsorption of sodium is dehydration produced by deprivation of water. And the strongest stimulus to thirst and

to reabsorption of water is excessive concentration of sodium salts in the extracellular fluid. The question of the volume and location of the circulating blood and its regulation still requires open-minded inquiry.

I should not be altogether ingenuous if I did not admit that nervous control of renal function, of which physicians are only beginning to become aware and which has been neglected in this discussion, might prove to be an important factor in the phenomena of circulatory disorders.

Finally, sodium is spoken of more freely than available data warrant. The measurement of sodium has been a protracted, meticulous procedure for which few laboratories are equipped, and which is ill adapted to the regulation of therapy in the clinic. Sodium figures have been interesting chiefly in retrospect, too often as records of errors in the evaluation of other evidence. It has been generally assumed (and I plead guilty on this score) that the concentration of sodium can be estimated from the sum of the concentrations of bicarbonate and chloride with the aid of astute clinical observation. It is, of course, recognized that in diabetic acidosis and advanced renal insufficiency replacement of bicarbonate and chloride by other anions (ketone acids, phosphate, sulfate and so forth) invalidates such estimations.[25] The frequency with which such estimations fail in heart failure has been less widely appreciated. In fact, the concentration of sodium in the serum in heart failure has been more discussed than investigated.

The nature of all the discrepancies between sodium and bicarbonate and chloride in heart disease cannot be discussed for lack of time. Only one matter is truly relevant to the subject, the concentration of sodium salts in the serum in heart failure. If retention of these salts were the primary event in heart failure, serum sodium in this condition should be regularly elevated or in the upper normal range. Furthermore, the logical first measure in the treatment of cardiac edema would be the administration of mercurial diuretics, which specifically inhibit reabsorption of sodium salts by the kidney. This has indeed been advocated. It has even been claimed, without any adequate evidence, that these compounds have a beneficial action upon the heart itself. In a certain proportion of patients with heart failure, serum sodium is slightly elevated. But in another group, for reasons that have not been altogether elucidated, it may be subnormal.[26] In the latter, mercurial diuretics are distinctly contraindicated.

A man of sixty-three, with long-standing heart failure, having neglected to take his digitalis, was admitted to the hospital with a puffy face, orthopnea, distention of the neck veins, pulmonary congestion, bilateral hydrothorax, a greatly enlarged heart, an enlarged liver, probable ascites and massive generalized edema. The venous pressure was equivalent to about 200 mm. of water, the circulation time (decholin) was 40 seconds, and the vital capacity 1.5 liters. He was given 1 cc. of mercuhydrin intravenously on admission, which provoked no diuresis. In fact, he voided only 150 cc. of urine during the next thirty hours. On the morning after admission he seemed much worse. The blood nonprotein nitrogen was found to be slightly elevated, whereas the serum albumin, chloride and sodium were greatly reduced. Digitalization was begun at once, and on the following day, since chloride, sodium and bicarbonate were still low, he was given 500 cc. of 3 per cent sodium chloride intravenously. His condition improved strikingly, and his urine volume increased. Within three days his weight had decreased 7 kg., and venous pressure had fallen to normal. In this case mercurials were obviously contraindicated. The low sodium presumably contributed, as it will, to the circulatory failure. There are exceptions even to the rule that salt must be withheld in heart failure. It is possible that digitalis alone would have been effective. The state of the patient was so critical that it was impossible to conduct the experiment one step at a time. Such cases constitute a challenge to those who argue for primary retention of sodium chloride in heart failure. Their incidence must not be overlooked by the clinician. Measurement of sodium should be more generally practiced as soon as simple and practical flame photometers become available.

* * *

My object has been not so much to solve, as to pose, the problems of cardiac edema. I hope that I have clearly distinguished in the discussion fact from speculation. I have tried to emphasize that in the clinic, as in the laboratory, plausibility is no substitute for sound reasoning based on fundamental scientific principles; that generalization from particulars is dangerous; and that no single organ or system in a complex integrated organism can be considered *in vacuo* apart from the whole.

References

1. Starling, E. H. Fluids of body. *Herter Lect.* (New York, 1908). Chicago: W. T. Keener and Co., 1909.
2. McCarrell, J. D., Thayer, S., and Drinker, C. K. Lymph drainage of gall bladder together with observations on composition of liver lymph. *Am. J. Physiol.* **133**:79-81, 1941.
3. Gregersen, M. I., and Rawson, R. A. Disappearance of T-1824 and structurally related dyes from blood stream. *Am. J. Physiol.* **138**:698-707, 1934.
4. Smith, H. P. Fate of intravenously injected dye (brilliant vital red) with special reference to its use in blood volume determination. *Bull. Johns Hopkins Hosp.* **36**:325-342, 1925.
5. Ferrebee, J. W., Leigh, C. C., and Berliner, R. W. Passage of blue dye T-1824 from blood stream into lymph. *Proc. Soc. Exper. Biol. & Med.* **46**:549-553, 1941.
6. Hahn, P. F., et al. Red cell and plasma volumes (circulating and total) as determined by radio iron and by dye. *J. Exper. Med.* **75**:221-232, 1942.
7. Gibson, J. G., 2nd, Peacock, W. C., Seligman, A. M., and Sack, T. Circulating red cell volume measured simultaneously by radioactive iron and dye methods. *J. Clin. Investigation* **25**:838-847, 1946.
8. Walker, A. M., Bott, P. A., Oliver, J., and MacDowell, M. C. Collection and analysis of fluid from single nephrons of mammalian kidney. *Am. J. Physiol.* **134**:580-595, 1941.

9. Shannon, J. A. Control of renal excretion of water: effect of variations in state of hydration on water excretion in dogs with diabetes insipidus. *J. Exper. Med.* 76:371-386, 1942. Control of renal excretion of water: rate of liberation of posterior pituitary antidiuretic hormone in dog. *Ibid.* 76:387-399, 1942.

10. Heller, H. Renal excretion of pituitary (posterior lobe) extracts. *Nature* 151:502, 1943.

11. Robinson, F. H., Jr., and Farr, L. E. Relation between clinical edema and excretion of antidiuretic substance in urine. *Ann. Int. Med.* 14:42-54, 1940.

12. Teel, H. M., and Reid, D. E. Observations upon occurrence of antidiuretic substance in urine of patients with pre-eclampsia and eclampsia. *Endocrinology* 24:297-310, 1939.

13. Ralli, E. P., Robson, J. S., Clarke, D. H., and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of liver. *J. Clin. Investigation* 24:316-325, 1945.

14. Elkinton, J. R., and Taffel, M. Prolonged water deprivation in dog. *J. Clin. Investigation* 21:787-794, 1942.

15. Winkler, A. W., Danowski, T. S., Elkinton, J. R., and Peters, J. P. Electrolyte and fluid studies during water deprivation and starvation in human subjects, and effect of ingestion of fish, of carbohydrate, and of salt solutions. *J. Clin. Investigation* 23:807-815, 1944.

16. Verney, E. B. Absorption and excretion of water: antidiuretic hormone. *Lancet* 2:739, 1946.

17. Warren, J. V., and Stead, E. A., Jr. Fluid dynamics in chronic congestive heart failure: interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. *Arch. Int. Med.* 73:138-147, 1944.

18. Landis, E. M., Brown, E., Fauteux, M., and Wise, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise. *J. Clin. Investigation* 25:237-255, 1946.

19. Perera, G. A. Increased plasma volume in cardiac insufficiency: its correlation with right-sided failure. *J. Clin. Investigation* 24: 708-711, 1945.

20. Stewart, H. J. Mechanism of diuresis: alterations in specific gravity of blood plasma with onset of diuresis in heart failure. *J. Clin. Investigation* 20:1-6, 1941.

21. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as primary cause of edema. *J. Clin. Investigation* 25:389-400, 1946.

22. Stead, E. A., Jr., and Ebert, R. V. Shock syndrome produced by failure of heart. *Arch. Int. Med.* 69:369-383, 1942.

23. Schwartz, W. B. Treatment of shock accompanying myocardial infarction. *Am. Heart J.* 33:169-174, 1947.

24. McCann, W. S., and Brown, H. R., Jr. Use of concentrated plasma protein solutions in congestive heart failure. *Internat. Clin.* 1: 109-115, 1942.

25. Hald, P. M., Heinsen, A. J., and Peters, J. P. Estimation of serum sodium from bicarbonate plus chloride. *J. Clin. Investigation* 26: 983-990, 1947.

26. Peters, J. P. Unpublished data.

NAIL CHANGES IN FUNCTIONAL AND ORGANIC ARTERIAL DISEASE*

EDWARD A. EDWARDS, M.D.†

BOSTON

IT IS the purpose of this paper to show that the nails undergo specific changes in vasospastic and in organic peripheral arterial disease and are sensitive indicators of the severity of the underlying state.

Raynaud[1] made more detailed notation of such changes than subsequent writers did. Thus he stated that the nails may be cast off by vascular disease attacking them at their "root"; that growth of the nail stops during an episode of necrosis, and that they begin to grow when this episode is over, then showing a transverse depression; and that ulceration of a digit may give loss of support of the nail at its extremity and result in a curving of the nail round the end of the digit. Heller's[2] more recent monograph gives the impression that nail changes occur infrequently in vascular disease, consisting mainly of necrosis or ulceration concomitant with that of the digit. He does mention that in scleroderma the nails are frequently involved by atrophy, thickening and deformation. Pardo–Castello[3] states that in peripheral vascular disease, disturbances are frequent, with Beau's lines (transverse depressions indicating periods of retarded growth), partial loosening, atrophy, distortion and, finally, destruction by gangrene.

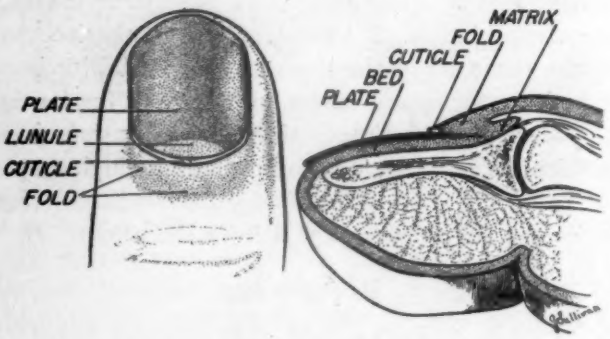

FIGURE 1. *Normal Anatomy of the Nail.*

Before these changes are considered it may be useful briefly to describe the normal appearance of the nail and its associated parts. Reference may first be made to a longitudinal section of the nail (Fig. 1). The nail plate, ordinarily referred to simply as the nail, consists of dead cornified material pushed distally by the growth of the parent cells of the nail matrix, and lying on the epithelial nail bed. The surface of the digit shows the nail plate overlain by the skin, known here as the *nail fold*, which is arbitrarily divided into proximal and lateral parts. The nail fold is cemented to the nail plate by its surface cornified cells, visible as the translucent cuticle. The cuticle is thicker and more evident at the proximal nail fold, with a width of 1 mm. or less. It is all that remains of the eponychium that in the early embryo covers the entire nail plate. One may also note the lunule, the white crescentic area of nail bed seen through the proximal end of the nail plate in the fingers.

*From the Department of Surgery, Tufts College Medical School. Aided by a grant from the Charlton Research Fund, Tufts College Medical School.

†Instructor in surgery, Tufts College Medical School; clinical associate in anatomy, Harvard Medical School; consultant in peripheral vascular diseases, Joseph H. Pratt Diagnostic Hospital; surgeon-in-charge, Vascular Clinic, Boston Dispensary.

Observations

Nail Changes in Vasospastic Conditions

These consist of a remarkable thinning of the proximal nail fold, with a more gradual merging into the translucent cuticle. The latter membrane is greatly widened, and does not end abruptly at its distal or free edge, as it does normally. Instead it extends out for several millimeters, to merge almost imperceptibly with the nail plate (Fig. 2).

Figure 2. *Typical Lesion in Arteriospastic Disease. Widening of the cuticle ("pterygium") and thinning of the nail fold are observed in Raynaud's disease of long standing.*

The cuticle lesion described is the one termed "pterygium" by dermatologists.

Concerning it, Pardo–Castello[3] states:

> This epidermal membrane may in some pathologic conditions advance 2 to 3 or more millimeters over the nail plate and become adherent to its outer surface. This is seen accompanying such conditions as peripheral neuritis, leprosy, sclerodactylia, and atrophy of the nails of different nature. It is a common condition in the last two toe nails in apparently normal persons. . . It is also seen in onychophagia.

This picture may be found in apparently all varieties of vasospastic disease, including the cold, stiff, splinted extremity, more outspoken vasospastic states and, most characteristically, Raynaud's disease and scleroderma (Fig.2, 3, 4 and 5).

Figure 3. *Pterygium in Disseminated Scleroderma.*

I am convinced that pterygium is characteristic of the severer grades of Raynaud's disease, especially in the fingers. It is an apparently constant finding in fingers in which secondary scleroderma has set in, and it seems to be an accurate herald of coming scleroderma if that change has not yet become evident. Moreover, pterygium is just as characteristic in primary or generalized scleroderma as in the secondary form.

Pterygium may be seen in the toes, but less often and less pronounced than in the fingers (Fig. 4). The fairly common normal pterygium of the toes, which is not characterized by thinning of the nail fold described above, is excluded from this discussion.

Figure 4. *Pterygium in the Great Toes in a Patient with Post-Trench-Foot Syndrome.*

I have not seen the lesion developing in the presence of purely organic obstruction. On the other hand, it can be demonstrated in a variety of diseases, in all of which there are vasospastic reflexes mediated through the sympathetic nervous system. One may postulate either that the effect is due to the direct influence of nerve on tissue or that the mechanism involves a differential diminution in the various parts of the digital circulation. The latter possibility would be consistent with the known diminution in these diseases in the blood flow through the nail fold, from which the cuticle grows.

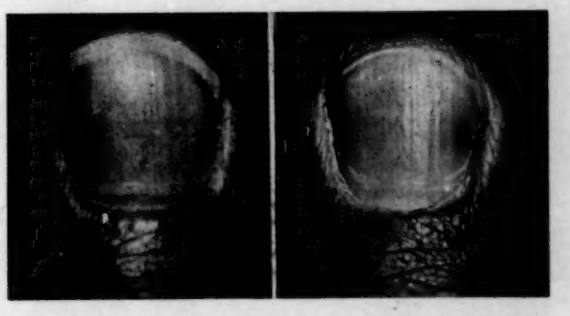

Figure 5. *Correction of the Nail Lesion in Raynaud's Disease. In the photograph on the left, ten days after sympathectomy, typical changes are still present. In that on the right, five weeks after operation, the nail fold has resumed its normal thickness, and the cuticle its normal, sharply delimited character.*

Whatever the mechanism, sympathectomy promptly does away with the lesion. In three or four weeks after the operation, the nail fold has become full, and the new cuticle is seen growing

in its normal, sharply delimited manner. Remnants of the old cuticle are seen adhering to the nail plate (Fig. 5).

Nail Changes in Organic Arterial Occlusion

Severe ischemia, whether resulting from arteriosclerosis or from the less common thromboangiitis obliterans, gives rise to a distortion of the growth of the nail plate (Fig. 6). I have no data to offer on the likelihood that the same lesion occurs in other, less common, varieties of organic occlusion. There are no accompanying nail-fold and cuticle changes as seen in the vasospastic diseases. The linear growth is retarded to the extent that the nail may not have to be trimmed for months or years. The nail plate may gain in thickness, becoming heavy and rough. The roughening is usually caused by the presence of transverse or eccentrically placed, parallel ridging. The nail plate is darkened, but it is impossible to say whether this is due to a contained pigment or to external soiling of its roughened surface. The thickened and darkened plate effectively shuts off the underlying nail bed from view. The distortion of nail growth may take the form of a claw nail (onychogryposis).

FIGURE 6. *Typical Lesion in Organic Arterial Disease, Showing Distortion, Thickening and Pigmentation of the Nail Plate in Ischemia Due to Arteriosclerosis.*

FIGURE 7. *Improved Nail Growth in a Case of Buerger's Disease Four Months after Sympathectomy.*

The distorted plates are being displaced by a more normal growth. The distortion of the nail of the index finger (left) was associated with osteomyelitis of the terminal phalanx.

An increase of blood supply, obtained by any means, is signalled by a return of the roughened nail to normal growth (Fig. 7 and 8). This results in a rapid distal displacement of the old mis-shapen nail by a new, more normal portion, through which may now be seen the nail bed, of a variable pink.

FIGURE 8. *Improved Nail Growth in Buerger's Disease.*

In the upper photograph, taken after suction-pressure treatment, the deformed nail is being pushed forward by a more normal growth. In the lower photograph of the same patient, taken after a relapse two years later, a similar correction of growth followed the administration of testosterone propionate.

FIGURE 9. *Diffusion of the Lunule in a Patient with Multiple Congenital Arteriovenous Communications of the Forearm, Hands and Fingers.*

The contrast between the old diseased nail and the newer, more normal portion serves as a striking indication of the improvement of the circulation. It is clinically useful to utilize the reversal of nail change in evaluating the benefit of therapy.

An occasional change in pronounced ischemia due to a variety of diseases is so-called diffusion of the lunule (Fig. 9). This appearance is described by Pardo-Castello as follows:

> Diffusion of the lunula is a very common condition in leprosy and other dystrophic conditions of the extremities. The lunula loses its sharp anterior limit, spreads forward, and seems to invade all the nail bed. This is due to the formation in the nail bed of a granular layer loaded with keratohyalin, and finally results in defective cornification. Many cases of total leukonychia may be explained in this manner.

The distortion of nail growth gives rise to no apparent pain. The patient may complain of pain about the nails, however, if the ischemia is extreme. In such cases the local tissues are hyperesthetic, and the slightest pressure gives rise to severe pain. In the toes, the pain may be interpreted by both the patient and the doctor as due to ingrown toenail. Ingrown toenail may or may not be present, but it should be realized that the very recent onset of such symptoms in an older person is usually due to an ischemic hyperesthesia. Relief from the pain will be obtained by the cessation of weight bearing and an increase in arterial flow. Operative interference on real or imagined ingrown toenails in the presence of ischemia may result in gangrene.

Nonspecific Lesions in Functional and Organic Disease.

In cases of great severity, the nail plates may be loosened and painlessly shed. This fact was mentioned by Raynaud[1] in several of his cases.

Primary infections of the nails are not seen with any characteristic frequency. On the other hand, the acral ulceration of arterial disease may involve the nails, with resultant distortions of their structure. Chronic subungual infection may also be seen in relation to the frequent ischemic osteomyelitis of the terminal phalanges (Fig. 7).

Summary

The nails show specific pathologic changes in both arteriospastic and organic arterial diseases and are sensitive indicators of the severity of the underlying state. In arteriospastic states, changes that may be grouped under the dermatologist's term of pterygium are described. They consist of a thinning of the nail fold and a widening of the cuticle. The normal abrupt demarcation between nail fold and cuticle, and between cuticle and nail plate is lost. Sympathectomy quickly restores the nail fold and cuticle to normal.

In organic arterial disease the nails do not show these changes. There is rather a thickening, roughening, and darkening of the nail plate, which hides the nail bed. An increase in arterial circulation by any means gives rise to a more nearly normal growth of the plate. Less specific changes include the growth of claw nails, or the presence of "diffusion of the lunule" in organic states, and the loosening and shedding of the nail plate in severe disease of either vasospastic or organic origin.

Painful nails are often an expression of the hyperesthesia of severe ischemia, in which operations for ingrown toenail usually cause gangrene.

Primary infections of the nails are uncommon in peripheral vascular disease, but the nails may be involved in acral ulceration, or may show subungual abscess over an osteomyelitis of the terminal phalanx.

372 Marlborough Street

References

1. Raynaud, M. *De l'asphyxie locale.* 174 pp. Thèse, Paris, 1862.
2. Heller, J. Die Krankheiten der Nägel. In *Handbuch der Haut- und Geschlechtskrankheiten.* Edited by J. Jadassohn. Vol. 13. Part 2. Berlin: Julius Springer, 1927.
3. Pardo-Castello, V. *Diseases of the Nails.* Second edition. 193 pp. Springfield, Illinois: Charles C Thomas, 1941.

A POSTOPERATIVE MASTECTOMY DRESSING*

LEO H. POLLOCK, M.D.†

KANSAS CITY, MISSOURI

THE postoperative dressings of a radical mastectomy wound may be assisted and simplified by discriminate application of adhesive tape. This easy method, which I have used for many years, is not mentioned in the literature.

A strip of plain or elastic adhesive, 2.5 to 4.2 cm. wide, is flamed. The strap is started over the lower

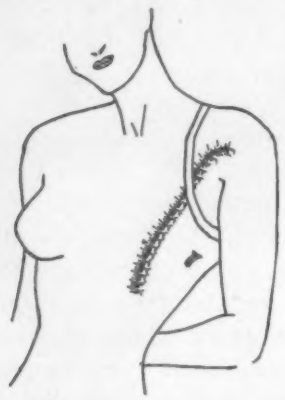

FIGURE 1. *Curved Adhesive Strap, Molding the Skin to the Chest Wall in a Longitudinal Incision.*

This supports the posterior axillary fold to lessen the tension on the suture line. It greatly decreases the padding needed to obliterate the dead space.

aspect of the scapula. It is brought across the axilla by one hand as the other presses the posterior axillary fold anteriorly and upward. The medial

FIGURE 2. *Adhesive Strap Approximating the Upper Skin Flap to the Chest Wall When a Transverse Incision Is Used.*

This minimizes the use of voluminous dressings.

or upper skin flap is pushed toward the incision as the adhesive curves upward in the infraclavicular depression resulting from the removal of the pectoral muscles. It then crosses the ridge of the shoulder to end over the upper part of the scapula. A thin piece of sterile gauze may be placed over the incision under the adhesive.

The procedure works very well with any type of skin incision, either transverse or longitudinal. The attachment of the skin flaps to the chest wall is helped by scattered mattress sutures placed between them and by various types of pressure dressings. The important point in the method is the selective molding of the skin to the concavity in front of the head of the humerus before the outer

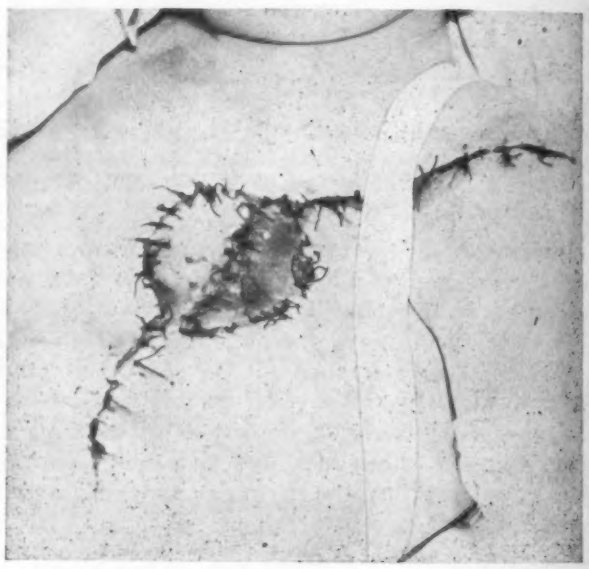

FIGURE 3. *Left Radical Mastectomy Wound on the Sixth Postoperative Day.*

The adhesive strip fits into the depression resulting from the removal of the pectoral muscles. This has obliterated the dead space. The full-thickness skin grafts are holding well. Tension on the edges is removed by the strip supporting the posterior axillary fold.

dressings are applied (Fig. 1). It minimizes the voluminous padding to obliterate the dead space. Also, the amount of padding is materially decreased by the application of similarly curved adhesive strips over it (Fig. 2). The strap supports the weight of the posterior axillary fold, which may be a dehiscing force in an obese or muscular patient. It lessens the circular constrictions on the chest that accompany swathes, binders and broad transverse adhesive straps relied upon for pressure.

*From the Surgical Service, Menorah Hospital.

†Attending surgeon, Menorah Hospital.

The condition of the wound on the sixth day after operation is shown in Figure 3.

Should a defect develop in the suture line, this method of strapping promotes healing by helping to approximate the edges and decreasing edema of both the skin and granulation tissue. One need not remove the outer dressings to take out the drain. A heavy silk suture may be attached to the end of the drain and then fastened lineally to the lower edge of the outer pad. The drain may be extracted by pulling on the loose end of the thread.

1310 Bryant Building

FAVISM*

ALBERT P. ROSEN, M.D.,† AND JAMES J. SCANLAN, M.D.‡

PROVIDENCE, RHODE ISLAND

FAVISM as a cause of hemolytic anemia, though not uncommon in the Mediterranean basin, especially in Sardinia and Sicily, is rare in the United States. The first case to appear in the American literature was reported by McRae and Ullery[1] in 1933. Since then individual cases have been reported by Hutton,[2] Eads and Kash,[3] Josephs[4] and Wharton and Duesselmann.[5] It is the purpose of this report to review briefly the clinical features and possible etiology and to describe a typical case, as well as to call attention to the fact that the fava bean (broad bean) in addition to being imported is now being grown in this country. It appears very probable that many more cases would be discovered here if this entity were considered in the differential diagnosis of acute hemolytic anemia.

The syndrome, caused either by ingestion of the seed or by inhalation of the pollen of *Vicia faba*, is characterized by gastrointestinal complaints and sudden appearance of hemolytic anemia, followed by hemoglobinuria, jaundice and vascular collapse.

Symptoms occur after the inhalation of the pollen, in a matter of minutes to a few hours; after ingestion of the bean there is a delay of five to forty-eight hours. The symptoms vary in severity. A mild form is not uncommon, resulting in malaise, yawning, headache, vertigo, nausea, vomiting, diarrhea, pyrexia, abdominal pain and, at times, loss of consciousness. These symptoms usually disappear in a few days. The severer form includes hemoglobinuria, marked pallor and icterus. The urine becomes red or black. The icterus increases, and hepatomegaly and splenomegaly usually ensue. Recovery takes place within a week, but the symptoms may persist for several weeks. The blood picture during the attack reveals a marked reduction in red cells with anisocytosis, reticulated cells, polychromatophilic cells and erythroblasts. There is a marked leukocytosis during the first week. Death occurs almost only in children, and the mortality is 8 per cent.[6]

Three theories have been proposed in the pathogenesis of favism: infectious, toxic and allergic. Luisada,[6] in his comprehensive review of the Italian literature, presents a fair amount of evidence pointing to allergy as the mechanism in this syndrome. Robinson[7] also favors allergy; peripheral-blood and bone-marrow smears in 3 of his cases revealed an increase in eosinophilic cells.

Sensitivity to the fava bean can be determined by skin tests, the optimum time being about six weeks after an attack. Apparently there is a refractory state during which skin tests are negative even in persons sensitive to the products of *V. faba*.

Josephs[4] points out that the disease appears to have a racial background identical with that of Cooley's anemia. Possibly this peculiar racial background serves to explain a manifestation of allergy that is certainly unique.

The treatment consists essentially of whole-blood transfusions to correct the anemia and of supportive measures. Epinephrine is recommended if there is vascular collapse.

CASE REPORT

T. F. (C. V. C. H. 70704), a 5-year-old boy of Italian descent, entered the hospital on February 15, 1948, because of abdominal pain, red urine and jaundice of 30 hours' duration.

On the afternoon before entry, the child complained of crampy abdominal pains and vomited. That evening he complained of headache. The cramps continued intermittently throughout the night, and he had two loose, brown stools, neither of which appeared abnormal. His mother noted that his urine was "wine colored," a color that persisted with each micturition until admission. The temperature was 101°F., and he was observed to be "very pale." On the next morning it was noticed that his skin was yellow, and this became increasingly evident as the day wore on. The cramp-like abdominal pains recurred and he began to yawn frequently. A physician advised hospitalization.

The past history yielded no positive information concerning recent exposure to toxic fumes or chemicals. The patient had been apparently well until the sudden gastrointestinal upset. There were no cases of malaria in the family or immediate neighborhood. He had received no injections or transfusions, and there was no history of familial anemia or of syphilis in either parent. However, two years before admission, at the age of 3, he had had a similar episode of "jaundice" accompanied by nausea, vomiting, fever and the passage of red urine. This had lasted for 2 weeks and had cleared up spontaneously without medication. A further note

*From the Pediatric Service, Charles V. Chapin Hospital.

†Fellow, Emma Pendleton Bradley Home; formerly, assistant clinical director, Charles V. Chapin Hospital.

‡Intern, St. Joseph's Hospital.

of interest in the history was the fact that the patient had had eczema in infancy and had a known allergy to eggs.

Physical examination revealed an acutely ill, pale and drowsy boy. He sighed and yawned conspicuously. There was a marked generalized lemon-colored icterus with an underlying pallor of the skin; the mucous membranes and scleras were markedly icteric. There was a moderate generalized lymphadenopathy. The eyes, ears, nose and throat were normal. The lungs were clear to percussion and auscultation. The heart sounds were loud and forceful, and there was a Grade III precordial systolic murmur. The apical rate was 130, there was a normal sinus rhythm, and the heart was not enlarged to percussion. There was generalized abdominal tenderness and some muscle guarding. The spleen edge, which was sharp and notched, was palpable 5 cm. below the left costal margin. The liver was not palpated, but there was a suggestion of a mass in the right upper quadrant. The genitalia, extremities and nervous system were normal.

The temperature was 101.6°F. by rectum, and the blood pressure was 98/68.

Examination of the blood revealed a red-cell count of 1,520,000, with a hemoglobin of 38 per cent (5.5 gm.), and a white-cell count of 33,150, with 71 per cent neutrophils, 9 per cent large lymphocytes, 19 per cent small lymphocytes and 1 per cent eosinophils. The hematocrit was 35 per cent. The smear showed red cells with marked central pallor, anisocytosis, poikilocytosis, some target cells and spherocytes. There was moderate polychromatophilia and a reticulocyte count of 3.8 per cent.

The urine, which was Burgundy-red and had a specific gravity of 1.016, gave an acid reaction and contained 1.2 gm. of albumin per 100 cc. of urine. It was packed with red cells, occurring singly, in clumps and in casts.

The patient was given 500 cc. of compatible whole blood in addition to 5 per cent glucose in water and saline solution. The next morning his color had improved noticeably, and the icterus had diminished in intensity. He was more alert and took soft-solid foods with relish. A second urinalysis yielded Burgundy-red urine, with a specific gravity of 1.025 and a neutral reaction, and containing 1.5 gm. of albumin per 100 cc. and rare red cells and a few white cells in the sediment.

The clotting time was 2 minutes, 33 seconds, and the bleeding time was 1 minute, 58 seconds. A cell-fragility test showed initial hemolysis in 0.38 per cent sodium chloride and complete hemolysis in 0.32 per cent.

The blood chemical findings were normal except for a slightly elevated icteric index.

X-ray films of the skull demonstrated some prominence of the digital impressions but no "hair-on-end" appearance or thickening of the skull table. The left hand had 4 carpal ossification centers, and the right hand 3 centers.

The temperature showed a mild elevation until the 4th hospital day, when it became normal. Recovery was uneventful. The icterus disappeared, the spleen receded, and the heart murmur became less prominent. The red-cell count on the 5th hospital day was 3,950,000, with a hemoglobin of 75 per cent. Daily urinalyses showed a rapid clearing and a gradual decrease in albumin content, as well as a disappearance of the cellular elements.

The etiology of the hemolytic episode was unexplained until at the suggestion of an attending physician* an investigation into the history was made pertaining to the ingestion of fava beans. It was found that on the day before the onset of the illness, the patient's grandmother had cooked a quantity of fava beans, of which the patient had eaten four plates full. Further questioning revealed that the child had eaten fava beans just prior to the attack of icterus 2 years previously.

Discussion

The diagnosis of favism appears to have been warranted in this case on the basis of the history of two attacks of hemolytic anemia associated with the ingestion of fava beans and the physical and laboratory findings. Skin-testing agents for fava-bean sensitivity were not available at the time of writing so that permission was requested of the mother, which she refused to grant, to feed the boy a few fava beans. In view of the 8 per cent mortality rate, the issue was not pressed.

Luisada[6] believes more cases will be seen in the United States for the following reasons: the fava bean is now cultivated in New York, New Jersey, Illinois and California; a large Mediterranean population lives in certain parts of the United States, and the fava bean is a staple article of the diet; and the beans are being imported from Italy as a canned food.

The beans can be purchased in practically all the grocery stores in the Federal Hill section of Providence, which is populated mainly by people of Italian background.

Apparently, the syndrome also affects peoples of Jewish stock. The bean is frequently used by them under the name of "bub." The case reported by Eads and Kash[3] occurred in a male of Spanish-Jewish descent. Robinson[7] reports 6 cases in Palestine in which the patients were at first thought to have Lederer's anemia. An interesting point in his paper may be worth repeating. There is evidence that the incidence of blackwater fever increases in March, the time of the ripening of the fava bean, and yet malaria in March is uncommon. This supports the observations of other authors[6] that a good many cases of favism have been misdiagnosed as blackwater fever because of the hemoglobinuria and splenomegaly. Wharton and Duesselmann[5] believe that some of the cases of hemolytic anemia classified as Lederer's anemia may possibly be explained by an allergic phenomenon similar to or identical with favism.

Apparently, the disease can affect any age group. Of the 5 cases reported in the American literature, 3 were in adults,[1–3] and 2 were in children.[4, 5] The case presented above is the sixth reported in the United States and the third case that involved a child.

All the American cases occurred in males, which follows the European trend in that males are affected much more frequently than females.

Summary

A case of favism in a five-year-old boy is presented with a review of the clinical features. More cases of this syndrome will be seen in the United States because the fava bean is now cultivated here.

*We are indebted to Frank J. Jacobson, M.D., for suggesting favism as the possible diagnosis.

References

1. McRae, T., and Ullery, J. C. Favism: report of case. *J. A. M. A.* **101**:1389-1391, 1933.
2. Hutton, J. E. Favism: unusually observed type of hemolytic anemia. *J. A. M. A.* **109**:1618-1620, 1937.
3. Eads, J. T., and Kash, R. M. Favism: report of case. *U. S. Nav. M. Bull.* **41**:1720-1724, 1943.
4. Joseph, H. W. Favism. *Bull. Johns Hopkins Hosp.* **74**:295-298, 1944.
5. Wharton, H. J., and Duesselmann, W. Favism: short review and report of case. *New Eng. J. Med.* **236**:974-977, 1947.
6. Luisada, A. Favism: singular disease chiefly affecting red blood cells. *Medicine* **20**:229-250, 1941.
7. Robinson, P. Favism in children. *Am. J. Dis. Child.* **62**:701-707, 1941.

MEDICAL PROGRESS

PREGNANCY TESTS (Concluded)*

STANLEY L. ROBBINS, M.D.†

BOSTON

Friedman Test[10]

This technic was developed within a few years of the original mouse test and represents a modification employing rabbits in place of mice. It is based on the principle that female rabbits ovulate only upon stimulation by the male and, therefore, do not spontaneously ovulate or have corpora hemorrhagica. The administration of gonadotropin likewise produces ovulation and corpora hemorrhagica, and hence their presence after the administration of urine indicates a positive pregnancy reaction.

The technic for the performance of the test is composed of the intravenous administration of first morning urine into the ear vein with examination of the ovaries forty-eight hours later. The amount of urine administered and the number of doses employed vary widely from the original description of six doses of 4 cc. each over a two-day period to a single injection of 15 to 20 cc. of urine. Some laboratories are employing blood serum (6 cc.) in place of urine with equally satisfactory results.[86] Inspection of the ovaries may be performed under anesthesia, and if the reaction is negative, the animal may be re-used, and the cost per test thus reduced.

The great advantage that this modification has over the Aschheim–Zondek test is its relative speed — forty-eight hours as compared to four to six days. Although follicle hemorrhage may occur as early as fourteen hours after the administration of the urine, it only becomes a definite reaction in twenty-four to forty-eight hours.[87] Larger doses of chorionic gonadotropin prove fruitless in speeding this change. Because of its relative speed the test has achieved widespread acceptance with invariably good results. The numerous reports in the literature cite accuracy from 100 per cent[10] to 98–99 per cent.[61–64] Certain drawbacks to the use of this technic are worth noting. It is necessary to have constantly at hand a colony of isolated, relatively large female animals, each weighing 3 or 4 pounds. The animals are very sensitive to toxic urines and are easily killed, and, thirdly, occasional focal hemorrhages that occur may closely resemble true ovulatory hemorrhages, making the test difficult to read.

Ovarian Hyperemic Tests

One of the first effects of chorionic gonadotropin on the ovaries of immature rats is the development of a superficial hyperemia. This change appears within two hours and reaches its peak in sixteen to twenty-four hours, long before corpora hemorrhagica or corpora lutea appear. On the basis of this ovarian color change, numerous procedures have been developed, perhaps best referred to as the two-hour rat test,[20, 21] the six-hour rat test[17] and the twenty-four-hour rat test.[12–16]

As indicated above, the color changes produced in a positive pregnancy reaction begin in two hours. At that time the color change is subtle and is based on a comparison of the faint hyperemization of the ovary with the pale serosa of the other viscera. Since the urine in this two-hour technic is administered intraperitoneally, a resultant possible nonspecific inflammatory reaction of the other viscera may mask the slight ovarian color change. A great danger exists, therefore, of false-negative results, reported by Zondek, Sulman and Black[88] to be as high as 45 per cent. As more time elapses, the color change becomes more definite, but even the six-hour and twenty-four-hour tests have failed to gain wide acceptance because of this difficulty in reading the endpoint. It can best be summed up by saying that in the hands of the original investigators the procedures appear to give good results, but difficulty in reading the endpoint, for all but the most experienced, makes it of limited value to laboratories in general.

Frog Tests

As long ago as 1933 Shapiro and Zwarenstein[11] presented the first report of the use of the female South African frog in pregnancy diagnosis, based upon work by Hogben.[89] Subsequent references by these authors occurred in the ensuing two years,[65, 66] and in 1938 Elkan[67] introduced the procedure in England. Three years later Weisman and Coates[68] popularized this technic in the United States. Since that time numerous reports have appeared receiving the test with great enthusiasm. Accuracy is cited as between 96 and 100 per cent.[90–93]

The test is based on the fact that the female *Xenopus laevis*, like the rabbit, never ovulates un-

*From the Mallory Institute of Pathology, Boston City Hospital.

†Assistant professor of pathology, Boston University School of Medicine; instructor in pathology, Tufts College Medical School; instructor in pathology, Harvard Medical School; assistant pathologist, Mallory Institute of Pathology, Boston City Hospital.

less stimulated either by the male or by the administration of gonadotropic hormone. Hence, isolated female frogs, when injected with urine from pregnant women, react to a positive test by the extrusion of hundreds of grossly visible ova, usually in twenty-four and occasionally in forty-eight hours. If no eggs appear the test is negative. In either case, after an appropriate rest (four weeks after a positive test and one week after a negative test) the animal can be re-used throughout a ten-year to eleven-year life. Recently, blood serum has been found to be as useful as urine in this technic.[94] The advantages of this procedure are numerous. The endpoint is definite and simple to read — the presence or absence of ova. The speed exceeds that of the Friedman test. Re-use of the animals and their ease of maintenance make the procedure not only adaptable for small laboratories, but also very cheap. In 1946 Parker, Robbins and Loveridge[95] succeeded in successfully rearing these animals in the United States and demonstrated the complete usefulness of these captive-bred amphibia for pregnancy diagnosis, thus removing the objection of the unavailability of these animals in this country. The sole remaining objection to the widespread use of this technic is the need to obtain and concentrate large volumes of urine, 40 to 80 cc., for each frog, a fastidious and protracted procedure. As pointed out above, in the course of breeding experiments it was noted that the male *Xenopus laevis* reacted to gonadotropic hormone and that this reaction was readily visualized by microscopical examination of the cloacal fluid. This reaction was further notable in that the male frog appeared to be considerably more sensitive to chorionic gonadotropin than the female, smaller quantities of urine sufficing to produce reactions in the male. Whereas concentrates of 40 cc. of urine were required to produce a reaction in the female *Xenopus laevis*, 10 cc. of whole urine sufficed for the South American male *Bufo arenarum* and 5 cc. of whole urine for the North American male *Rana pipiens*. The technic of the test is essentially the same, using either the North or the South American frog. Only the quantities of substances administered differ. With the North American *Rana pipiens* 5 cc. of whole urine or 5 cc. of blood serum[25, 56] is administered to each of a pair of frogs. Cloacal fluid from the external cloacal orifice, obtained by use of a glass pipette, is examined unstained by the hanging-drop technic, one and two hours after injection. The reactions are clear cut, all or none, comprising the presence of spermatozoa in a positive test and their total absence in a negative test. As can be noted, the reaction develops within two hours, frequently in half an hour, and therefore the entire test sometimes requires only two and a half hours to perform. Re-use of the frogs is possible, but their low cost and the difficulty in feeding them make such use both unnecessary and inadvisable. In the present state of knowledge this reaction in the male *Rana pipiens* appears to be due to the presence of the luteinizing chorionic hormone. The frog does not appear to react to follicle-stimulating hormone derived from menopausal urine. An accuracy of 98 per cent has been achieved in this laboratory with this pregnancy test. Although this procedure still requires the use of animals, it most closely approaches in simplicity and speed the concept of a test-tube technic that is easy to read. Its value in the differential diagnosis of acute conditions of the abdomen with relation to ectopic pregnancy or any other emergency in which speed is of greatest urgency is obvious.

Pregnanediol Test of Guterman[39]

Of the several chemical procedures reported to be of use in the diagnosis of pregnancy, the only one that appears to hold any great promise is the test developed by Guterman.[39] This test is based on the observation by Venning and Browne[40] that pregnanediol is present throughout pregnancy although in low concentration in the first trimester. The test comprises essentially an extraction of the acid hydrolyzed pregnanediol and the development of a color complex by the addition of sulfuric acid. Reports of the accuracy of this procedure have been somewhat equivocal. Guterman[77] has recently cited his accuracy as 92 per cent in 248 tests, whereas Morrow and Benua[42] and McCormack[41] imply that low-titer urines may give false-negative reactions, and nonpregnant women with delayed menses may give false-positive reactions owing to the high level of corpus luteum hormone in the secretory phase of the menstrual cycle. The test has the fundamental disadvantage of dealing with the lowest titer of hormone when early diagnosis is required, in contrast to the extremely high titers of the last trimester when the diagnosis is obvious clinically. In conditions other than pregnancy associated with a high gonadotropic excretion, such as moles and chorionepitheliomas, this test is very useful since it is said to remain negative and therefore to differentiate these conditions from pregnancy.[77]

In the recent literature occasional reference is made to the various skin tests listed, to the histidine-excretion tests and to the prostigmine test. However, since these procedures in their present state of development contribute nothing to the diagnostic methods described above, they have not been described in any detail.

Discussion

Any discussion of pregnancy tests must begin by emphasizing certain facts. All bio-assay technics, which comprise the commonly used tests for pregnancy, depend in essence upon the presence in the urine or the blood stream of chorionic gonadotropic

hormone, the result of functioning chorionic epithelium in contact with the blood stream. It does not necessarily imply a living fetus. These tests, therefore, cannot distinguish between normal or abnormal pregnancies or tumors containing chorionic epithelium. It is possible in cases of intrauterine death of the fetus or of inevitable missed abortions to have viable, functioning chorionic tissue maintain a positive pregnancy reaction for some time. Moreover, even after all the functioning tissue has died, time is required for the excretion of the hormone already produced. Depending on the original level of hormone that existed, this time may vary from several days to a week. Rarely, cases of persistence of detectable chorionic hormone have been encountered months after total removal of a hydatid mole. When fetal death is suspected clinically and a positive pregnancy reaction is encountered, a repeat assay should be performed some time later, when the hormone is almost certain to have become lower or to have disappeared from the urine or serum. It is also obvious that in extremely early pregnancy negative reactions may be encountered, frequently termed as "false-negative reactions," when the test is performed before the prolan titer has had time to rise to a detectable level. In general, the Aschheim–Zondek test, the Friedman and the frog tests are able to detect early pregnancy approximately seven days after the first missed period. However, since hormone titers of pregnancies show great variation from person to person, this time required for an adequate luteinizing hormone level to develop cannot be stated as an absolute time period applicable to all.

In many cases in which the test has failed to conform to the course that the pregnancy followed, the reaction has been termed an error in diagnosis. This use of the term "error" is unfortunate since at the time of the performance of the test the hormone titer may have been at some transitional level when the titer was either rising or falling. A test performed one or two weeks later would have dealt with a newly established level that would have conformed to the future course of the gestation.

The second point to be remembered is that no pregnancy test — and for that matter no laboratory test — is infallible. Reports constantly emphasize the closeness with which these various diagnostic procedures approach 100 per cent accuracy, rather than the percentage of errors inherent in each technic. Thus, although a test may be 99 per cent accurate, the one error in a hundred is small solace to the physician or patient who falls heir to this sole discrepancy. Technical errors and insensitive or physically unfit animals contribute to errors in diagnosis. Moreover, well documented cases of normal pregnancy are cited in which it was impossible to obtain a positive Aschheim–Zondek test.[96] Such cases are fortunately extremely rare; nonetheless they contribute to the so-called errors in pregnancy diagnosis. It is perhaps only fair to point out that in the absence of these pregnancy reactions it has never been established that the so-called "negatively reacting" normal pregnancies ever elaborated any chorionic gonadotropin. So much for the errors inherent in the laboratory diagnosis of pregnancy.

The question whether urine or blood serum is a better substance to use in any of these diagnostic procedures is an important one. To the best of my knowledge at present they may be used interchangeably. Smith and Smith[96] have long advocated the use of serum because unextracted urine is frequently toxic, killing all the animals to which it is administered. This death of laboratory animals is a most bothersome problem in laboratory technic since time is lost, valuable animals destroyed and almost invariably before a successful test has been achieved the specimen that is being assayed is used up and time must be wasted getting a new specimen. Serum, by contrast, appears to be remarkably free of this objection. Although it might at first appear that the titer of hormone should be higher in the serum than it is in the urine, this conclusion is not correct. Zondek et al.[88] state on the contrary that the titer of hormone appears in lower concentration in the serum than in the urine. This fact is particularly true when first morning concentrated urine specimens are used, since the amount of hormone excreted in a twenty-four-hour interval is uninfluenced by the volume of urine and hence reaches higher levels in concentrated urines. It is for this reason that when urines are to be used for pregnancy diagnosis it is advisable to restrict fluids and use the first morning urine. Notwithstanding this differential in hormone levels, if blood serum is titered on frogs or rats against first morning urine in an unselected series of normal pregnancies, the serum appears to give results as good as if not better than those obtained with urine — that is, it appears to give higher titers. It is possible that this difference in hormone level is more apparent than real and may be due to either a renal threshold holding back serum hormone and producing a low urine titer or to the fact that the urine may, by its toxic effects, depress the sensitivity of the animals. In any event, in the interests of a less toxic, more constant source of hormone, blood serum appears to be preferable to urine.

Is it possible to say that any one of the tests described above is better than the others? No, since each procedure has its own peculiar advantages that suit it best to specific indications.

The Aschheim–Zondek test, despite the time it requires for performance, is to this day unsurpassed for accuracy, especially when the equivocal ovarian changes are controlled by microscopical slide examination. In view of the dual changes possible

in the rat ovary, diagnosis of weak titers make the Aschheim–Zondek test of great value in detecting early gestations and complications of pregnancy such as miscarriages. The value of this weakly positive Aschheim–Zondek test has been brought out by Tenney and Parker.[97] In a series of 60 patients weakly positive tests, performed at a time when they should have been strongly positive, indicated in every case a complication of pregnancy. It is highly likely that assays performed on this same series with other technics would have yielded only completely valueless negative results.

The Friedman test has been up to the present time one of the most widely used tests because of its great accuracy and simplicity of performance. However, of recent date the shortage of rabbits and their rising cost have seriously discouraged many laboratories from the use of this animal. It was, in fact, these difficulties that catapulted the female *Xenopus laevis* into such wide usage. Not only was the female-frog test somewhat faster, but it was moreover, because of the possible re-use of the frogs, considerably cheaper. The male-frog technics at present appear to hold the greatest promise. The animals are widely available, easy to keep and cheap, and a positive diagnosis may be returned while the patient waits. Certainly, in cases of ectopic pregnancy, this procedure may prove life saving.

The determination of pregnanediol in the urine is the only chemical test for pregnancy of any significant value. It is unfortunate that its sensitivity is low in very early pregnancy and that its specificity has been questioned in cases of delayed menstruation. Further analyses are required to evaluate this technic more adequately.

No discussion of the laboratory diagnosis of pregnancy would be complete without a consideration of the functioning tumors, chorionepithelioma and hydatidiform mole. Inasmuch as these tumors usually develop after an abortion, miscarriage or pregnancy, their laboratory differential diagnosis from normal pregnancy is most important. It is well known that both of these tumors elaborate and excrete large amounts of gonadotropin, usually considerably more than that encountered in a normal pregnancy. Differences in the titer of hormone, as obtained in our laboratory, can best be expressed as pregnancy produces luteinizing hormone in the thousands of rat units, hydatidiform mole in the tens of thousands, and chorionepitheliomas in the hundreds of thousands. It is impossible to express these general differences any more specifically since enormous variation in titer may exist at different ages of the same tumor, and certainly between different tumors. The factors important in determining the levels of hormone that a given tumor will produce include the amount of chorionic tissue present, its proximity to blood supply and, most of all, the important question of whether it is a functioning tumor capable of elaborating hormone. Not only are rare pregnancies incapable of elaborating chorionic gonadotropin but also rare hydatids and chorionepitheliomas may elaborate virtually no hormone. The exact explanation for this curious behavior is not certain; however, it is possible that the absence of this capacity is a function of the degree of anaplasia of the tumor. The well known tendency of these tumors to undergo necrosis is another cause of wide differences in hormone production. It must therefore follow that no arbitrary hormone titers for these tumors can be specified. In the differentiation of these tumors from pregnancy, on the basis of the level of hormone produced, careful consideration to the possible duration of the pregnancy must therefore be taken into account. At the peak production, titers of luteinizing hormone up to 15,000 rat units per twenty-four hours may be found in pregnancy. It is entirely possible for small hydatid moles or chorionepitheliomas to produce less hormone than this amount.[98] On the other hand, titers of hormone over 25,000 rat units for a twenty-four-hour sample and certainly over 50,000 rat units, according to the standards employed at our laboratory, almost certainly indicate the presence of either a mole or a chorionepithelioma.

In brief, quantitative assays of hormones may or may not be diagnostic of themselves, and, in general, they are best used as confirmatory evidence rather than diagnostic criteria. It should be emphasized that assays for hormonal titers or levels should be performed only on twenty-four-hour urine samples. Quantitative urine assays on spot samples of urine are of little value.

More difficult than the problem of differentiating pregnancy and neoplasms is that of following patients after surgical removal of one of these lesions. A widespread misconception prevails that after successful removal of a mole or a chorionepithelioma the hormone promptly disappears from the circulating blood and urine within a matter of a few days. It is not appreciated that the time required for the gonadotropin to disappear is extremely variable, depending not only upon the original height of the hormone level but also upon the rate of excretion of the hormone. As pointed out above, levels of detectable gonadotropin have persisted for months after successful removal of a mole.[99] Any single quantitative determination, then, is of limited value since it may represent persistence of hormone from the preoperative level. It is much better practice to follow the hormone level by serial quantitative titer assays so as to determine whether the hormone is increasing or decreasing in the blood. Falling levels, however long after the removal of a tumor they occur, can only signify that no new hormone production has occurred and that, therefore, the patient is free of functioning chorionic epithelium. Any reversal of

this fall or rise in level obviously indicates recurrence of tumor. It is for these reasons that simple qualitative urine tests for the detection of the mere presence of a positive reaction have no value in postoperative tumor diagnostic work and are definitely to be discouraged since they may well cause totally unnecessary alarm.

References

86. Evans, N., and Krajian, A. A. Note on Friedman pregnancy test using blood serum. *Am. J. Clin. Path.* Tech. Sect. **8**:97, 1944.
87. Boehm, E. E. Use of zipper in Friedman test. *Am. J. Clin. Path.* Tech. Sect. **5**:168, 1941.
88. Zondek, B., Sulman, F., and Black, R. Hyperemia effect of gonadotropins on ovary: and its use in rapid pregnancy test. *J. A. M. A.* **128**:939-944, 1945.
89. Hogben, L., Charles, E., and Slome, D. Studies of pituitary: VIII. Relation of pituitary gland to calcium metabolism and ovarian function in *Xenopus*. *J. Exper. Biol.* **8**:345-354, 1931.
90. Scott, L. D. Concentration and detoxification of human urine for biological pregnancy diagnosis. *Brit. J. Exper. Path.* **21**:320-324, 1940.
91. Foote, E. C., and Jones, G. E. S. Evaluation of Hogben pregnancy test. *Am. J. Obst. & Gynec.* **51**:672-677, 1946.
92. Elkan, R. E. New test for pregnancy. *Post-Grad. M. J.* **22**:87-93, 1946.
93. Weisman, A. I., and Coates, C. W. Frog test (*Xenopus laevis*) for pregnancy: report on 1000 tests over period of 4 years of study. *West. J. Surg.* **52**:171-174, 1944.
94. Rosenfeld, S. S., and Rosenfield, V. W. Reaction of *Xenopus laevis Daudin* (South African clawed frog) to human pregnancy serum: new test for pregnancy. Preliminary report. *J. Lab. & Clin. Med.* **29**:527-529, 1944.
95. Parker, F., Jr., Robbins, S. L., and Loveridge, A. Breeding, rearing and care of South African clawed frog (*Xenopus laevis*). *Am. Naturalist* **81**:38-49, 1947.
96. Smith, O. W., and Smith, G. V. Tests for pregnancy. *J. Clin. Endocrinol.* **4**:551, 1944.
97. Tenney, B., Jr., and Parker, F., Jr. Significance of weakly positive Aschheim-Zondek test. *New Eng. J. Med.* **218**:561, 1938.
98. Boycott, M., and Smiles, J. M. Diagnosis of hydatidiform mole by biological assay. *Lancet* **1**:1428-1430, 1939.
99. Payne, F. L. Hormone studies in presence of hydatidiform mole and chorioepithelioma. *Surg., Gynec. & Obst.* **73**:86-95, 1941.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 34361

Presentation of Case

A six-year-old schoolboy entered the hospital because of persistent vomiting.

Until three weeks before admission the patient had no complaints. He then began to have anorexia and became moderately constipated. Eight days prior to admission he began to vomit on the average of one to three times a day. The vomiting was preceded by episodes of crampy, periumbilical pain. No fever had been present prior to admission.

Physical examination revealed a listless, rather poorly nourished boy lying flat in bed, with respirations of 40 to 50 per minute. A diffuse forceful apex impulse was visible extending almost to the anterior axillary line. A gallop rhythm was present, without murmurs or friction rubs. The remainder of the examination was negative. One observer felt the liver edge 3 cm. below the costal margin.

The temperature was 99.2°F., and the pulse 120. The blood pressure was 90 systolic, 66 diastolic.

Examination of the blood revealed 12.5 gm. of hemoglobin and a white-cell count of 13,000, with 51 per cent neutrophils, 34 per cent lymphocytes, 2 per cent monocytes and 13 per cent band forms. Urinalysis showed a specific gravity of 1.030, with no albumin, sugar or formed elements in the sediment. The serum nonprotein nitrogen was 23 mg., and the total protein 5 gm. per 100 cc. The prothrombin time was 18 seconds (control, 15 seconds). The sedimentation rate was 4.5 mm. per hour (normal, up to 20 mm. per hour). The Schick, blood Hinton and tuberculin (dilution of 1:1000) tests were negative for diphtheria bacilli.

A throat culture was negative for beta-hemolytic streptococci, diphtheria bacilli and pneumococci. An electrocardiogram showed a sinus tachycardia, with a rate of 160, and a PR interval of 0.13 second. The QRS complex was 0.07 second, and the T waves were flat in Lead 1 and inverted in Leads 2 and 3.

An x-ray film of the chest showed a marked increase in density in both lungs, more marked at the bases. The heart was enlarged, particularly to the left, with a cardiothoracic ratio of 11.5:18.5. A small amount of fluid was present in both costophrenic sinuses. The cardiac pulsations were diminished but regular. Diaphragmatic motion was free and equal. A plain film of the abdomen showed the liver to be slightly larger than normal. The spleen was not enlarged.

On the third hospital day the patient complained of pain below the tip of the sternum. The pulse rose to 160, and he appeared to be in shock. Following this episode he was placed in oxygen, and digitoxin was started, with definite improvement for the next few hours. During the next few days he remained about the same while digitoxin and oxygen were continued. A repeat electrocardiogram showed a rate of 140, with a PR interval of 0.14 second.

On the sixth hospital day the child was found to be drowsy, and later a right hemiplegia involving the face, arm and leg was noted. A lumbar puncture revealed a clear fluid and an initial spinal-fluid pressure equivalent to 170 mm. of water. No cells were present, and a Pandy test was negative. Repeat x-ray films at this time disclosed considerable mottled density in the right lung, radiating from the right hilar area peripherally. On the left, behind the heart, was a large area of dense lung. The

bronchial markings throughout this region were observed to terminate very close to the origin of the left main bronchus, which was elevated above its usual position. The area of density lay within the posterior portion of the lower lobe. There was a small area of emphysema adjacent to the lower lateral heart margin. In the upper portion of the left lung mottling of the lung parenchyma was noted, similar in character to that noted on the right. There was a small amount of fluid within the pleural space on the right, particularly notable within the minor septum.

Penicillin and aspirin were administered without appreciable effect. The temperature, which had become elevated prior to the onset of hemiplegia, remained slightly elevated during the remainder of the hospital course, fluctuating between 99.6 and 100.4°F. The white-cell count showed a rise to 17,500, with 90 per cent neutrophils. The patient continued to fail slowly, and the nonprotein nitrogen rose to 72 mg. per 100 cc. He was seen by numerous consultants during the next few days. On the sixteenth hospital day he died, approximately eight hours after a second cerebral accident.

Differential Diagnosis

Dr. Sidney Farber*: May I ask for a cardiac expert to interpret the electrocardiograms?

A Physician: They could represent pericarditis.

Dr. Farber: I would like to ask for one or two bits of information before going on. The first question has to do with the character of the vomitus, whether it appeared in relation to meals and whether there was any blood in it. Also was there any blood in the stools at any time?

Dr. Edward P. Wallace: The vomitus was bile stained and related to eating. The boy took fluids but did not vomit while in the hospital. One stool specimen was normal.

Dr. Farber: He did not lose enough chloride to cause you to replace them artificially?

Dr. Wallace: One chloride determination was normal.

Dr. Farber: I wonder if we might see the x-ray films.

Dr. Stanley M. Wyman: The films of the chest show a definitely enlarged heart without characteristic configuration. One cannot trace the posterior border adequately, but it appears to protrude backward considerably farther than usual. Throughout both lung fields there is a poorly defined, hazy mottling extending peripherally almost to the extreme lung margins. At this time the pleural spaces appear free of fluid. The liver margin comes down to the crest of the ilium; the liver may be slightly enlarged. The next examination five days later shows the heart shadow still larger but the film was taken with the patient lying on his back, and the x-ray tube was closer to the patient, causing some magnification. The right-lung field has not changed materially, nor has the left upper lung. In the left-lower-lung field, however, behind the heart is a sharply defined area of density without any visible pulmonary markings in this region. The bronchi coming to this area extend a distance of 3 cm. and terminate in an irregular fashion. The left main bronchus appears definitely elevated and compressed. The question arises whether the density lying behind the heart is in the lung or adjacent to the lung in the mediastinum. Again, I cannot identify the upper posterior heart border in the lateral view. There is very little, if any, fluid in the pleural spaces.

Dr. Farber: Is the consolidation of the lung consistent with an infarct?

Dr. Wyman: I cannot point to a definitely localized lesion to suggest infarct. The picture seems to be too diffuse and widespread and to emanate from the hilus.

Dr. Farber: Is there evidence of aspiration of vomitus, with occlusion of the bronchus in the next to the last film?

Dr. Wyman: It is conceivable, but I do not see any lung markings at all in that area. It would make me assume that the lung was "drowned"; yet I can trace the bronchus down a fair distance. I believe that fluoroscopically the heart showed diminished but regular pulsations.

Dr. Farber: I confess that I am a little more confused than when I read the history. Some of these x-ray findings are not what I would have anticipated from the history.

I can begin in several different ways. The first and most obvious is to begin with the vomiting. The patient was well until the onset of the illness, which began five weeks or so before he died. We must assume that he was well until that time. We assume also that he had no abdominal operation previously and that adhesions, volvulus and obstruction cannot have played any part in this history. Among the conditions that could be responsible for this picture we must mention congenital malformations and tumors of the bowel involving the duodenum or a duplication of the duodenum, jejunum or stomach. Vomitus preceded by periumbilical pain could be produced by pressure from without, by tumor or by infection of the bowel or an inflammatory process such as that found in sarcoidosis. I think we ought to consider whether we should think of neoplasm any further. The story is perfectly consistent with the occurrence of a tumor either within the wall of the bowel or in the region of the intestinal tract with compression of the bowel. If we were to think of the most common tumors to do this, we would mention lymphosarcoma, with or without leukemia, the embryoma of the kidney or unattached in the kidney region and neuroblastoma. It is conceivable for lymphoma particularly to involve all

*Pathologist-in-chief, Children's Hospital, Boston.

these areas one after another, and I think that a tumor would have been excluded by palpation of the abdomen, and certainly x-ray studies would have been instituted to determine whether one was present.

The second area of involvement appears to have been the heart. If we have some suggestion from the electrocardiogram of pericarditis, of pericardial effusion particularly, after the child had been in the hospital for three days, the episode of pain below the tip of the sternum might have been due to increase in pericardial fluid and pericarditis. The pain might also have been due to coronary obstruction with infarct of the heart or an extremely diffuse myocarditis. We have been seeing the latter frequently caused by an agent that is probably a virus rather than a bacterium. The heart shows definite involvement without evidence of interventricular or interauricular defect, congenital malformation or involvement of the valves.

The third area is the lung, and I am more perplexed now than on reading the description. I thought from the description that we were dealing with either an infarct or abscess or reaction to aspiration of vomitus. To explain the brain changes one could consider the possibility of metastatic abscess from the lung.

I mentioned previously the possibility of sarcoid involving the bowel as being responsible for the vomiting. There, too, we can find a possibility of involvement of the lungs and brain. We had such an experience recently in a child who had this disease and then hemiplegia many years after the initial bowel involvement.

This child had no evidence of a marked infection. The temperature was never high; near the end it was approximately normal, and there was very little change in the white-cell count. Yet the possibility of infection must be entertained seriously. The only infectious disease that might account for the changes would be subacute bacterial endocarditis, and we would have to assume involvement of the bowel with infarct. We are not given any evidence that that occurred — no blood in the stool and no other sign of infarct. But involvement of the bowel, the heart, the lung and the brain can be explained entirely by subacute bacterial endocarditis.

I have not mentioned the other possibilities of vascular disease. If we assume vascular accident or infarct in the brain, we should mention periarteritis nodosa, which is capable of producing all these changes in various locations. We should mention rheumatic fever with arteritis and diffuse myocarditis, possibly occurring in an extremely early attack with no evidence of previous damage to the valves. If the child lost a great deal of fluid during these three weeks of vomiting, presumably dehydration might have been of great importance, and then the possibility of sinus thrombosis must be entertained, with secondary cerebral hemorrhage and necrosis.

I am afraid I have exhausted the list of probable causes of such a group of changes, and I fine nothing in the record that would permit me to make a positive diagnosis with any degree of confidence. I think that if I were to choose the most likely diagnosis to explain everything, I would choose rheumatic fever, rheumatic myocarditis, with arterial involvement in a number of places. I am not sure that would go with the pulmonary picture that we have demonstrated by x-ray examination. I think I would have to explain the brain hemorrhage, which this must have been, on the basis of arterial lesions in the brain on a rheumatic etiology or possibly secondary to the complication of the vomiting and rheumatic fever — also, aspiration abscess in the lung with metastasis to the brain. I can go no farther than that.

A Physician: What about the congenital heart disease?

Dr. Farber: That is what I had in mind when I mentioned subacute bacterial endocarditis superimposed on an interventricular or interauricular defect, which would be responsible for very few symptoms and would explain why nothing was picked up earlier.

Dr. Tracy B. Mallory: What was the diagnosis on the ward, Dr. Wallace?

Dr. Wallace: We thought that the patient had myocarditis, but we could not determine the etiology. We thought he probably had a thrombosis or infarction to account for the cerebral signs.

A Physician: Were any blood cultures taken?

Dr. Wallace: Two — and they were both negative.

Clinical Diagnosis

Acute myocarditis, type undetermined.

Dr. Farber's Diagnoses

Rheumatic fever, with rheumatic myocarditis and arteritis?

Subacute bacterial endocarditis, with multiple infarcts?

Aspiration of vomitus, with lung abscess and metastatic brain abscess.

Anatomical Diagnoses

Cardiac hypertrophy, idiopathic.

Cardiac mural thrombosis, both ventricles.

Embolism and infarction of lung, kidney, spleen (and brain).

Myocardosis, focal.

Endocardial thickening.

Focal necroses of liver.

Hydropericardium, slight.

Pericarditis, fibrous, localized.

Pathological Discussion

Dr. Mallory: Dr. Castleman scheduled this case for discussion, asked Dr. Farber to present the clinical side and me the pathological side, and then wisely left town. I wish that Dr. Farber were

discussing the pathological side because I have not the slightest idea what this boy suffered from. I can tell the anatomical findings quickly and briefly. There was an excess of fluid in the pericardium — 70 cc. — and a few fibrous adhesions. Microscopically a few lymphocytes were found in the epicardium. The heart was very much hypertrophied, being two and a half times the normal size. The valves showed a barely perceptible elevation here and there but no frank vegetations. The coronary arteries were normal. Microscopically the myocardium showed many small foci of absorption of muscle fibers of varying ages. One person who looked at the heart, knowing nothing of the age of the patient or the gross findings, said that it looked like coronary-artery disease. That was my first impression when I looked at it. The endocardium of the left ventricle was distinctly thickened, and overlying the endocardium at the apex of both left and right ventricles were numerous adherent, partially organized thrombi. So we had a source for embolism in both major and minor circulations. There was infarction of the lung. There was also a rather extensive focal atelectasis with overdilatation of the respiratory bronchioles and complete collapse of alveoli in many areas. There were infarcts of the spleen and kidneys, but we could find nothing to explain the episodes of abdominal symptoms. We did not have permission to examine the brain, but without much question emboli were there also.

I have no idea how this case could be put together in any specific disease. We have what seems to be a primary extensive thrombosis within both ventricles, overlying thickened but not actually damaged endocardium. Nowhere in the valves, endocardium or myocardium do we have anything remotely suggestive of Aschoff bodies to permit a diagnosis of rheumatic infection, and nowhere in the sections did we find a vascular lesion. We have a slide here. Perhaps Dr. Farber can look at it and name the disease for us. The muscle cells are frankly hypertrophied for a child of this age. Here is one of the little patches of absorption where the muscle fibers have disappeared, with little reticulum and capillaries left. Most of these are old enough so that the muscle fibers have disappeared. There are one or two acute foci elsewhere between the columnae carneae where the endocardium goes into the myocardium. We found thrombi in varying stages of organization. In some places the muscle cells are markedly vacuolated; some degree of vacuolization is not uncommon, but this would be considerably more than normal.

In the liver there was extensive necrosis with congestion, and I am unable to say that it was on a degenerative or toxic basis. In many lobules two thirds of the liver cells were dead.

Can you offer any suggestions, Dr. Farber?

DR. FARBER: No; usually when I have entertained people here as a pseudoclinician, I comfort myself by going back to the microscope. Here I have no such comfort. We have had examples of diffuse endocardial damage with emboli breaking off, without any suggestion from post-mortem examination concerning the exact nature of the underlying disease.

A PHYSICIAN: Nothing is said about a murmur.

DR. WALLACE: No murmur was ever heard.

CASE 34362

PRESENTATION OF CASE

A seventy-two-year-old widow was admitted to the hospital because of a fracture of the right femur.

Two weeks before admission the patient first noted pain in the right thigh when walking. Massages and local applications gave no relief, but she continued with her usual work of housekeeping. Two days previous to admission the right leg suddenly collapsed while she was walking. There was severe pain in the right thigh, and she was unable to walk. She was admitted to another hospital, where x-ray examination revealed a fracture of the right femoral shaft; she was then admitted to this hospital.

The patient had developed deafness at the approximate age of forty-five. A sister and a son had early deafness.

Physical examination revealed moderately severe deafness. The heart was slightly enlarged to the left. A loud, harsh, apical systolic murmur was widely transmitted. A thorough pelvic examination, though unsatisfactory, was essentially normal. There was tremendous swelling in the right midfemoral region, with crepitus, shortening and external rotation of the right leg. The hands showed mild rheumatoid changes at the metacarpophalangeal joints.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 80 diastolic.

The urine had a specific gravity of 1.022 and gave a + test for albumin, and the sediment contained 2 red cells, 20 pus cells, 10 epithelial cells and + bacteria per high-power field. It contained no Bence–Jones protein. The blood hemoglobin was 11 gm., and the white-cell count 13,300, with 80 per cent neutrophils, 11 per cent lymphocytes and 9 per cent monocytes. The nonprotein nitrogen was 29 mg., the calcium 9.9 mg., and the phosphorus 4 mg. per 100 cc.; the alkaline phosphatase was 4.4 units. The total protein was 5.3 gm. per 100 cc., with 3.61 gm. of albumin and 1.69 gm. of globulin. A cytologic study of a vaginal smear was negative.

An x-ray film of the right femur showed a transverse fracture through the middle third of the shaft, with the distal fragment displaced posteriorly for a distance equal to the diameter of the bone and over-riding 6 cm. The fracture was through a large cystic area in the middle third of the shaft, and

beneath this there were several small cystic areas. In one portion there appeared to be expansion and erosion of the cortex of the bone. An intravenous pyelogram was negative.

The patient was suspended in Russel's traction, and later a Kirschner wire was inserted in the proximal right tibia for traction. Further x-ray examination revealed numerous areas of diminished density within the calvarium, limited mainly to the diploe. The thoracic spine showed only scoliosis and moderate hypertrophic changes. Changes interpreted as metastatic involvement were seen in many ribs, and there was a fracture in the seventh rib. A suggestion of several lytic lesions was noted in the scapula and in the body of the left humerus. No lesions were seen in the lungs though they could not be ruled out. Several suggestive areas were seen in the left pubis and ischium, and a definite, rounded, lytic zone was present in the right wing of the ilium. A small cystic zone was visualized in the left carpal navicular. A repeat examination of the calcium and phosphorus showed no essential change from the initial examination. The alkaline phosphatase at this time was 1.7 units per 100 cc., and on one occasion the calcium was 12.6 mg. per 100 cc. The twenty-four-hour urinary-calcium excretion was 101 mg. On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Oliver Cope: The patient had a pathologic fracture in the midshaft of the right femur. The description of the physical examination gives no clue regarding the origin of the disease. Since the positive laboratory observations — cells in the urine, a slightly elevated white-cell count, a mild anemia, subnormal blood serum protein and an elevated blood serum calcium determination in one of presumably several determinations — are either inconsistent or bear no relation to bone disease, they must be dismissed as uninformative. The entire written record, therefore, is of no help in clarifying the diagnosis, and we must turn to the roentgenographic examination. Realizing the importance of the roentgenogram, Dr. Castleman allowed me the privilege of reviewing the available films before starting this discussion.

Before examining the films, let me tell you how I approach such a problem — how I classify bone disease according to its distribution. The distribution of disease in bone may be divided into four categories: generalized, segmental, localized and warm bone involvement. Generalized bone disease occurs when the stimulus to bone disease is truly general, as in endocrine diseases and nutritional deficiencies. In endocrine diseases the hormonal disturbances are registered throughout the skeleton. The common hormonal diseases in this category are hyperparathyroidism, hyperthyroidism, adrenal cortical hyperfunction, anterior pituitary disturbances and perhaps acute gonadal disturbances. The nutritional deficiencies have a generalized distribution because all regions of the skeleton are exposed equally to the deficiency. For example, vitamin D deficiency, giving rise to rickets in children and osteomalacia in adults, shows changes generalized in distribution. So also with vitamin C deficiency and protein deficiencies interfering with bone matrix.

In the segmental type of distribution the bone disease follows the distribution of a peripheral nerve or nerve root. The Albright syndrome, or fibrous dysplasia of bone, is the classic example in which the bone lesions are thus distributed. This disease has been termed disseminated, but though the lesions are often disseminated, the word is not critically descriptive.

Localized disease of bone may originate anywhere in the skeleton as a result of either primary osseous or primary marrow tumors. The primary osseous tumors are commoner in the younger age group and occur most frequently near the rapidly growing bone — that is, in close relation to an epiphysis. The primary marrow tumors are those arising in one of the various tissues encountered in bone marrow, such as the endothelioma of Ewing, the myelomas and hemangiomas. Since these tumors bear no true relation to bone tissue they are found anywhere in the bone, bearing no relation to epiphyses.

Warm bone disease is the type of distribution encountered when malignant tumors and lipoid dystrophies, having a primary origin outside of bone, spread to the skeleton. The use of the word "warm" has a theoretic reason: that malignant tissue spreading to bone grows best in the warm areas. Metastatic lesions from cancers of the thyroid gland, breast, kidney and prostate are found less commonly in the bones of the distal extremities, which are less well covered with muscle and fat and are colder than the centrally located bones. In the metabolic disturbances, such as the Schüller–Christian syndrome, a similar warm bone distribution is found.

This is a peculiar case because although at first sign the distribution appears to be generalized (films of the entire skeleton are not available), the primary lesion, that of predominant interest, the right femur, can fit only in the category of localized bone disease. Let us look at the films. Dr. Wyman, tell us where you see disease.

Dr. Stanley M. Wyman: As Dr. Cope has said, all the films are not available. The presenting bone, the right femur, shows this rarefied bone-expanding lesion without significant reaction about its margins. There is a pathologic fracture through the center of this area of rarefaction. Lower in the same bone there are multiple, rather sharply defined areas of rarefaction. They are lesions that expand the cortex somewhat.

Dr. Cope: They are clearly punched out. I think you will agree that some of the areas in the acetabulum and skull are sharp and well defined.

DR. WYMAN: Yes, there are some in the ribs, pelvis and skull. The bones of the hands show no definite lesion. The left femur appears essentially normal, what I can see of it.

DR. COPE: It is the right femur and the left acetabulum that are affected.

DR. WYMAN: The left femoral shaft is normal. The interesting thing about the films is that the uninvolved bone appears fairly dense and of good normal texture, especially for a woman of seventy-two years. It is unfortunate that she has no teeth so that we cannot examine the lamina dura.

DR. COPE: Let us concentrate on the right femur and for the moment forget the other bones. There are multiple lesions, and all are in the lower half. There is nothing that I can see in the upper half. Is that right?

DR. WYMAN: Yes.

DR. COPE: This distribution immediately eliminates a metastatic tumor. If these lesions came from the thyroid gland, kidney or breast, the lesion should be concentrated in the upper half of the bone. On this distribution, therefore, I exclude renal and the other metastatic tumors. I cannot see that it follows the skeletal distribution of the Albright syndrome. The right femur is the major area of illness, and yet there is nothing in the right side of the pelvis. There are lesions in the left acetabulum but none in the left leg. Films of the arms to go with those of the hands are missing. As there is a questionable lesion in a carpal bone on the radial side, if there were lesions in the radius and in the ulna, it would be conclusive of the Albright syndrome.

It is hard to explain the appearance in the skull if you do not agree to a tumor that is metastasizing.

There is inconsistency in the pattern with which we are dealing. I cannot go any farther on the evidence available than to say that this was a disease primary in bone.

What kind of primary tumor was it? Was it an osteogenic sarcoma? It obviously was not, for there was no bone formation. The patient's age is also against such a tumor. Because of the clearly punched-out areas, I am going to take another long shot and say that it was not a primary osseous tumor, but a tumor arising in the bone marrow. Was it a hemangioma? Was it an endothelioma of Ewing? This tumor is also not usual in patients of this age. What other kind of tumor could it have been? There are a variety, of course, that can arise.

DR. BENJAMIN CASTLEMAN: What did you have in mind so far as bone-marrow tumors are concerned? Do you mean tumors like lymphoma or myeloma?

DR. COPE: It could have been a myeloma. Multiple myeloma is ordinarily accompanied by a high total protein. This patient's total protein was 5.3 gm. per 100 cc., which is low, and one cannot get a lead from the record.

DR. BERNARD JACOBSON: Why do you exclude metastatic carcinoma?

DR. COPE: The distribution in the bones is wrong, and there is no primary lesion.

DR. JACOBSON: Did she have a pyelogram?

DR. COPE: Yes, but a negative pyelogram does not exclude a hypernephroma. There ought to be more metastases around the pelvis and fewer metastases at the lower end of the femurs if it were hypernephroma or carcinoma of the thyroid gland or breast. Dr. Castleman extracted myeloma out of me, and the skull picture is characteristic of myeloma. A few years ago we had a patient about whom everybody disagreed. The x-ray films of the skull were put on the screen and everybody took a shot at them. Dr. Albright and I said multiple myeloma, Dr. Sosman said hyperparathyroidism, and Dr. Holmes suspected some kind of hemangiomatous tumor because of the connection of the punched-out areas in the skull with the venous sinuses. It turned out to be metastatic hypernephroma, so that one can be wrong on the basis of the x-ray films. In the final analysis dependence has to be placed on a biopsy of a lesion. I have tried to present to you how I personally attack such a problem. Yet I know on the evidence one cannot be flat-footed about making a diagnosis.

CLINICAL DIAGNOSIS

Metastatic carcinoma.

DR. COPE'S DIAGNOSIS

Primary bone-marrow tumor.

ANATOMICAL DIAGNOSIS

Multiple myeloma.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: On the wards this was believed to be a metastatic tumor; myeloma was ruled out, as Dr. Cope suggested, by the low serum protein and the absence of Bence–Jones protein. A biopsy, however, did show a definite plasma-cell myeloma.

DR. COPE: That fits with the configuration in the skeleton. We have had myeloma with a normal protein and a normal Bence–Jones, and Dr. Aub pointed out to me that when a case is in remission and is not in an active phase of proliferation, the Bence–Jones and serum proteins may be normal. One could guess that this patient had had relatively inactive disease for some time. If she had adequate trauma to cause a fracture, myeloma would satisfactorily explain the whole picture.

DR. JACOBSON: I would not be so optimistic as Dr. Cope about the inactivity of the disease. About 40 per cent of the cases of myeloma have normal serum proteins. About 99 per cent have elevated serum globulin. This patient's globulin was repeated and was low. She had a low formol-gel test. This is the first case of multiple myeloma that I know of in this hospital with a normal globulin.

The New England
Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Owned by the Massachusetts Medical Society and Published Weekly under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D., Editor

Associate Editors

Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor
Robert O'Leary, Assistant Editor

Editorial Board

C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. James M. Faulkner, M.D.
Robert M. Green, M.D. Carroll B. Larson, M.D.
Dwight O'Hara, M.D. Francis D. Moore, M.D.
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.
Robert L. Goodale, M.D. Vernon P. Williams, M.D.
Chester M. Jones, M.D. Benjamin Castleman, M.D.
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

Subscription Terms: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

New England Advertising Representative: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

ENGLAND ABANDONS COMPULSORY VACCINATION

The Englishman, whose home is his castle, and who has for centuries stubbornly defended certain hard-won principles of personal freedom, does not give up his rights without a struggle. A respecter of the law, he still may evade a law that does not please him, and only extreme circumstances will force him to turn, as he has done, to an authoritarian form of government.

The National Health Service Act provides a surprising example of the way in which such a government can take away with one hand and give with the other. Restricting many of the rights of the freeborn Englishman in the practice of medicine, it gives to the entire population (perhaps a sordid boon) freedom from compulsory vaccination against smallpox.

This surrender of compulsion in vaccination is not a complete right-about turn, as the history of vaccination in England shows. Greenwood* briefly tells the story.

For ninety-five years, with various modifications, vaccination of infants has been compulsory in England. In the early years of this period the provisions of the law changed little, and something over 60 per cent of infants were actually vaccinated, with the percentage increasing until, about sixty years ago, the law was observed in the cases of nearly 90 per cent of the infants born. Opposition to the Act then became firmer, and the vaccination rate dropped back nearly to the original 60 per cent. At about the turn of the century public vaccinators were required to visit the homes of infants, and the rate rose again to 70 per cent, dropping with further modification of the Act, to approximately 35 per cent, where it has remained ever since.

Now, in the land of Jenner's birth and within a few months of the two hundredth anniversary of that event and of the announcement of vaccination approximately the one hundred and fiftieth, compulsory vaccination has been entirely abandoned.

The decline in vaccination that has led up to this startling decision is not, Dr. Greenwood believes, a consequence of antivaccination propaganda, but has resulted from two facts. The first is that few Englishmen under sixty have had any experience with severe smallpox, and the second that vaccination has been known to have severe consequences. Postvaccinal encephalitis, it is true, is extraordinarily rare, but it has occurred.

Compulsory vaccination, in Dr. Greenwood's opinion, would be returned if it could be demonstrated that an epidemic of severe smallpox would inevitably result from its neglect. Such a promise, fortunately, cannot be made. British experience has shown, on the contrary, that the introduction of classic smallpox into a poorly protected community does not automatically give rise to a major epidemic so long as means are at hand for the immediate vaccination of those willing to be vaccinated.

Endemic smallpox is thus invited, on the assumption that prompt vaccination will prevent sporadic

*Greenwood, M. End of "compulsory" vaccination. *Brit. M. J.* 2:22-24, 1948.

outbreaks of the disease from assuming major proportions. England, in this respect, may now be compared to a city that abandons fireproof building construction because of its fire-fighting equipment that should, under normal conditions, hold in check those conflagrations that are likely to occur.

PROGRESS IN THE TREATMENT OF LEPROSY

THE recently published report of the United States Public Health Service workers on their latest results with the chemotherapy of leprosy[1] is the most encouraging of any thus far recorded and holds out high hopes for the eventual eradication of this ancient scourge. These results are the reward for perseverance and for painstaking efforts in the face of many disappointments that might easily have resulted in discouragement and the abandoning of the project.

Included in the report from the Leprosarium at Carville, Louisiana, are the results of therapy with the sulfone drug in 371 patients of whom 317 were treated with promin or diasone for varying periods up to six years. In the rest, the treatment was abandoned for various reasons but only in a very few cases was this due to failure to tolerate the drug. Severe toxic reactions were encountered, but in most cases it was possible to maintain therapy by adjusting the dose and method of administration. It was found, for example, that prómin could not be tolerated in adequate doses when given by mouth. A change to intravenous injections permitted the continuation of therapy with favorable effects. It was usually necessary to start with a daily dose of 1 gm. and then to increase the amount until 5 gm. daily was given, and this gave the most consistently good results with a minimum of toxic effects.

The most frequent toxic manifestation encountered was a slow destruction of the erythrocytes. This complication could not be avoided, but its effect was counteracted by discontinuing treatment for one week after two weeks of daily intravenous injections. This resulted in fewer and milder types of toxic reactions and permitted a restoration of the blood cells and hemoglobin lost through the hemolytic action of the drug. Transfusions were not used, and the administration of iron and liver extract was seldom found necessary. Diasone had the advantage of being less toxic than promin by oral administration, but otherwise it gave similar untoward effects. Dosage of this drug had to be increased gradually until the patient built up a tolerance, and most patients were eventually able to take 0.3 gm. three times a day. With this drug, rest periods of two weeks every two months proved advisable, and liver extract and iron were sometimes needed to counteract the anemia.

That these efforts and the toxic effects encountered were justified is evidenced by the results. Only patients with lepromatous leprosy and mostly with far-advanced disease were subjected to the sulfone therapy, and the drug worked slowly, but the therapeutic effects were better than those obtained from any previous treatment tried at the Carville Leprosarium. Definite objective improvement seldom became manifest before six months of treatment, but thereafter it was progressive. The percentage of patients improved was in direct proportion to the duration and intensity of the treatment. After six months almost 25 per cent of the patients showed some improvement; after one year this percentage increased to 60, after two years to 75 and after three years to almost 100 per cent, and this was independent of the extent and stage of the disease when the treatment was undertaken. The percentage of bacterioscopically negative smears among treated patients was also in direct proportion to the duration of the treatment. During the first year, practically all the cases remained bacilliferous, but after four years of continuous intensive treatment the incidence of negative reports exceeded 50 per cent.

Of the entire group, 38 patients have been discharged with "arrested" disease, representing 12 per cent of all the patients treated with promin or diasone. During 1946, the number of patients discharged with arrested disease was more than double that of the annual average for the ten years prior to the institution of sulfone therapy and the number of deaths was less than half the average of the previous years.

Faget and Erickson[1] emphasize the fact that the ultimate value of sulfone therapy in leprosy is not

definitely established. It has been pointed out elsewhere[2] that the long, unsettled and unsatisfactory experience with chaulmoogra oil dictates that considerable caution be exercised in ascribing antileprotic qualities to any drug. The final judgment must await the test of time, which the Carville workers place at five to ten years or possibly even longer.

These results in leprosy have important implications in the treatment of tuberculosis. It is of interest that the drugs that have proved effective in leprosy have been all but abandoned in the treatment of tuberculosis since the introduction of streptomycin. This was due mainly to the toxicity of these drugs and the relatively small benefit apparently derived from them. On the other hand, streptomycin was shown in brief trials to give a temporary improvement in leprosy for only a few weeks and later had no further beneficial effects at a time when the toxic effects of the drug began to occur. For that reason streptomycin has not been widely used in leprosy, which is in contrast to its relatively successful and widespread use in the treatment of tuberculosis. The results of sulfone therapy in the treatment of leprosy should lend encouragement to renewed and more persistent efforts to apply these or similar agents in the treatment of tuberculosis either alone or in conjunction with streptomycin or other effective antibiotics that may become available.

References

1. Faget, G. H., and Erickson, P. T. Chemotherapy of leprosy. *J. A. M. A.* **136**:451-457, 1948.
2. Editorial: Leprosy. *J. A. M. A.* **136**:830, 1948.

PROFESSOR NEUBURGER IN AMERICA

Professor Max Neuburger, the world-renowned historian of medicine, who on December 8, 1948, will celebrate his eightieth birthday, has arrived in this country, where he plans to spend the years of his retirement. It is fitting that the medical profession send him greetings and take cognizance again of the illuminating contributions of this distinguished scholar.

In 1893 Neuburger received the doctorate of medicine from the University of Vienna, where he had been influenced by such teachers as Billroth, Meynert, v. Brücke, Nothnagel, Fuchs and Politzer. The title of extra. prof. of the history of medicine was conferred upon him in 1904, and in 1912 he became titular professor. The University of Vienna honored him with the degree of Doctor of Philosophy in 1917. From 1917-1938 he was professor, founder and director of the Institute of Medicine and Historical Museum at the University of Vienna. Since 1939 he has been a member of the staff of the Wellcome Historical Medical Museum in London, England, and during these years he has published papers on the relations between British and German medicine.

Forty-two years ago, Neuburger's *Geschichte der Medizin* was published in Stuttgart. Through the interest of Sir William Osler the book was translated into English by Ernest Playfair and was published in 1910 by the Oxford University Press. Osler expressed the thought that the work was particularly useful to English and American students.

Fielding Garrison called Neuburger the greatest philosophical historian of medicine, and Sigerist pointed out that Neuburger's book, monographs and articles were of full significance for our own day. These carefully weighed opinions were justified for at least two reasons: medical history as presented by Neuburger revealed itself as a pulsating living phenomenon supplementing thereby the then current approach, which focused attention upon the philologic analysis of historical texts; and developments in the history of medicine were now being treated by setting them into the background of general history and within the *Kulturgeschichte* with which they ordinarily blend.

Neuburger is unquestionably one of the pivotal figures in the history of medicine today. His writings exhibit high qualities of expansive, critical and well balanced thought. A few excerpts, which are applicable to present-day medical philosophy, from his masterful *History of Medicine* are pertinent:

> The economic requirements of the human intellect necessitate a grouping of isolated facts from different points of view; the thirst for knowledge renders imperative a clearer insight into the laws governing natural phenomena . . . biological research, cosmology and dialectics were all points on the circumference of a circle, the starting-point being taken at will.
>
> It is neither doctrines nor knowledge which raise the Hippocratic creed to the highest pinnacle of Greek medi-

cine and even make it the well-spring of medical science for all time: it is the conception of the medical vocation and the method of medical thought and action, true now as then.

On the heels of the conqueror with his rude soldierly virtues follows the ruler with his love of luxury and his aspiration towards refinement of manners and customs. This historical law finally compelled even the empress of the earth, invincible Rome, to lay down her arms before a yet more powerful sovereign in the shape of Greek culture.

The essence of Galenism, as contrasted with Hippocratism, consists in giving the physician, through general principles, a reliable guide for his procedure in any individual case.

Honored throughout the world for his scholarly achievements Professor Neuburger may be heartened to learn that American students and physicians recognize the salutary lesson of his life in terms of modesty, patience and dignity. We sincerely wish him continued good health and the spirit and energy to pursue his invaluable labors.

Bibliography

Editorial. Professor Max Neuburger. *Brit. M. J.* 1:1243,1948.

Kagan, S. R. Professor Max Neuburger: biography and bibliography. *Bull. Hist. Med.* 14:423-448, 1943.

Neuburger, M. *Essays in the History of Medicine.* Edited by Fielding H. Garrison. 227 pp. New York: Medical Life Press, 1930.

Idem. History of Medicine. Translated by Ernest Playfair. New York: Oxford University Press. Vol. I. 404 pp. 1910. Vol. II. 135 pp. 1925.

Sigerist, H. E. Tribute to Max Neuburger on occasion of his seventy-fifth birthday, December 8, 1943. *Bull. Hist. Med.* 14:417-421, 1943.

STORROW HOUSE

The Massachusetts General Hospital has announced the opening on August 9, 1948, of Storrow House, with ward, semi-private and private accommodations for convalescent patients. The conditions for admittance are reasonable: patients must be ambulatory to the extent of being able to go to meals and they must be persons who are strictly convalescent or simply in need of rest. No terminal or mental patients or alcohol or drug addicts are to be accepted.

Storrow House, a stately mansion situated on a hilltop in Lincoln, Massachusetts, within twenty miles of Boston, was the country home of the late Mrs. James J. Storrow. Fulfilling the wishes of his mother, her son, James J. Storrow, Jr., has presented the house and estate to the Hospital for the purposes outlined above. It is a source of gratification to the recipients of her generosity that Mrs. Storrow's benefactions have continued in this manner after her death.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

Pratt — William P. Pratt, M.D., of Quincy, died on August 15. He was in his seventy-second year.

Dr. Pratt received his degree from Tufts College Medical School in 1907. He was a member of the staff of Quincy City Hospital.

An aunt and three-step-daughters survive.

NOTICES

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

The American Society of Anesthesiologists will hold a joint meeting with the Ohio Society of Anesthesiologists October 1 and 2, 1948, at the Hôtel Commodore-Perry, Toledo, Ohio.

OREGON STATE MEDICAL SOCIETY

The annual meeting of the Oregon State Medical Society will be held in Medford from September 15 to 18 (secretary, Werner E. Zeller, M.D., Medical Dental Building, Portland 5, Oregon).

VERMONT STATE MEDICAL SOCIETY

The annual meeting of the Vermont State Medical Society will be held in Burlington from September 15 to 17 (secretary, T. H. Harwood, M.D., 128 Merchants Row, Rutland, Vermont).

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, September 9

Friday, September 10

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference. (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

Tuesday, September 14

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, September 15

*12:00 m.–1:00 p.m. Clinical Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

September 7–11. American Congress of Physical Medicine. Page 582, issue of April 15.

September 7–11. American Occupational Therapy Association. Page xv, issue of July 8.

September 9. Some of the Advances in Surgery. Dr. Frank H. Lahey. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

September 13–15. American Academy of Pediatrics. Olympic Hotel, Seattle, Washington.

September 14. New England Society of Anesthesiologists. Page 316, issue of August 19.

September 16–18. Vermont State Medical Society. Annual Meeting. Burlington.

September 20–23. American Hospital Association. Page 310, issue of February 26.

September 22. New England Conference of Industrial Physicians and Surgeons. Page 244, issue of August 5.

September 29. Mississippi Valley Medical Editors' Association. Page 170, issue of January 29.

October 1 and 2. American Society of Anesthesiologists, Inc. Notice above.

October 6–9. American Board of Ophthalmology. Page 170, issue of January 29.

October 18–22. American College of Surgeons. Page 34, issue of July 1.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

(*Notices concluded on page xiii*)